

FUNCTIONAL ALIPHATIC POLYESTERS BASED ON
CYCLOADDITION METHODOLOGIES

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ABSTRACT

ANDREW H. BROWN: Functional Aliphatic Polyesters Based on
Cycloaddition Methodologies

(Under the direction of Dr. Valerie Sheares Ashby)

Polyester degradation *in vivo* allows the construction of temporary biomedical devices for wound closure, implants, and cargo delivery. The commercially available polyesters for these purposes lack polar or reactive functional groups, inherently limiting the versatility and effectiveness of these technologies. Many attempts have been made to incorporate functional groups into polyesters, mostly based on ring-opening polymerization methodologies. In this work, step-growth polymerizations are combined with cycloaddition reactions to include functional groups in new monomers and polymers that could be useful materials in biomedical engineering. First, the Diels-Alder cycloaddition was employed to synthesize a new family of dicarboxylic acid and anhydride monomers from various dienes. Amorphous, hydrophobic polyesters were attained in high molecular weight, including polymers containing polar functionality (amines and ethers). Thermosetting reactions yielded elastomers with mechanical properties similar to soft tissue that degraded in a slow, linear manner. A second methodology was developed based on the copper(I)-catalyzed azide-alkyne cycloaddition, in which an azide-containing diester monomer was synthesized and incorporated into aliphatic polyesters. These materials were then reacted with amine-containing alkynes to yield polyesters grafted in high density. All materials were fully characterized to better understand the structure-property relationships.

To Mom and Dad & Jason and Jenny: for being there.

To Jonathan: for steadfast friendship.

To Emily: for the path we have taken.

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LIST OF ABBREVIATIONS

ADMET	Acyclic diene metathesis
AIBN	2,2'-Azobis(2-methylpropionitrile)
ATRP	Atom transfer radical polymerization
BCA	Bicinchoninic acid assay
Bn	Benzyl
Boc	<i>tert</i> -Butoxycarbonyl
BPO	Benzoyl peroxide
ϵ CL	ϵ -Caprolactone
mCPBA	<i>meta</i> -Chloroperbenzoic acid
D-A	Diels-Alder
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DCC	Dicyclohexylcarbodiimide
DEA	Diethyl adipate
DMF	<i>N,N</i> -Dimethyl formamide
DPBS	Dulbecco's phosphate buffered saline
DSC	Differential scanning calorimetry
DXO	1,5-Dioxepan-2-one
FBS	Fetal bovine serum
GPC	Gel permeation chromatography
HEMA	2-Hydroxyethyl methacrylate
HMA	<i>trans</i> - β -Hydromuconic acid

LLA	L-Lactic acid
LDA	Lithium diisopropylamide
MALDI-TOF	Matrix-assisted laser desorption ionization time-of-flight mass spectrometry
MDO	2-Methylene-1,2-dioxepane
MEM	Minimum essential medium
MLABn	Benzyl β -malolactonate
MR	Mass remaining
MTS	3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium
MWD	Molecular weight distribution
N ₃ A	Diethyl 2,5-diazidoadipate
NMR	Nuclear magnetic resonance
OCA	<i>O</i> -Carboxyanhydride
OD	1,8-Octanediol
PCL	Poly(ϵ -caprolactone)
pCMV-Luc	Plasmid cytomegalovirus; luciferase
PDI	Polydispersity index
PDLLA	Poly(DL-lactic acid)
PDMAEMA	Poly[2-(dimethylamino)ethyl methacrylate]
PDXO	Poly(1,5-dioxepan-2-one)
PEG	Poly(ethylene glycol)
PEI	Poly(ethylene imine)
PEO	Poly(ethylene oxide)
PGA	Poly(glycolic acid)

PHEMA	Poly(2-hydroxyethyl methacrylate)
PLA	Poly(lactic acid)
PLGA	Poly(lactic acid- <i>co</i> -glycolic acid)
PLLA	Poly(L-lactic acid)
PMLA	Poly(β -malic acid)
PMLABn	Poly(benzyl β -malolactonate)
PMMA	Poly(methyl methacrylate)
PS	Polystyrene
PTMO	Poly(tetramethylene oxide)
RCM	Ring-closing metathesis
RI	Refractive index
RLU	Relative light units
ROMP	Ring-opening metathesis polymerization
ROP	Ring-opening polymerization
TBDMS	<i>tert</i> -Butyldimethylsiloxy
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
TOSUO	1,4,9-Trioxaspiro[4.6]-9-undecanone
δ VL	δ -Valerolactone
Z	Benzyloxycarbonyl
2EG	Diethylene glycol
3EG	Triethylene glycol
4EG	Tetraethylene glycol

LIST OF SYMBOLS

$\langle M_n \rangle$	Number-average molecular weight
$\langle M_w \rangle$	Weight-average molecular weight
T_g	Glass transition temperature
T_m	Crystalline melting temperature
T_{cure}	Curing reaction temperature
ΔH_m	Enthalpy of melting
f_{av}	Average degree of monomer functionality
R	Universal gas constant
Q_s	Percent soluble fraction
ν	Crosslinking density
E	Young's modulus
σ	Ultimate stress
ϵ	Ultimate strain

Chapter 1

LITERATURE REVIEW OF FUNCTIONAL ALIPHATIC POLYESTERS

1.1 Background

Aliphatic polyesters such as poly(lactic acid) (PLA), poly(glycolic acid) (PGA), and poly(ϵ -caprolactone) (PCL) hydrolytically degrade in aqueous environments to molecules that can be metabolized by the body. This degradation, coupled with favorable mechanical properties and availability in high molecular weight, accounts for the use of these materials in temporary medical devices for the past several decades. Initial research in poly(β -hydroxy acid)s derived from bacterial fermentation yielded absorbable surgical sutures.¹ These synthetic materials were designed to replace catgut and other tissue-based materials whose properties can be inconsistent from batch to batch. Laboratory synthesis and processing of PGA² and PLLA³ sutures led the way for temporary biomedical devices synthesized from aliphatic polyesters.

As the field advanced, the types of devices synthesized from aliphatic polyesters expanded greatly. Drug delivery devices⁴⁻⁶ and tissue engineering matrices⁷ are among the most widely investigated applications of these materials, and researchers have sought specific polymer properties to improve device performance. Some of the parameters that require precise control are thermal properties, mechanical strength, solubility in water or organic solvents, degradation rates and drug release profiles.

The overwhelming majority of the absorbable polyester devices in the clinic are composed of PLA, PGA, and/or PCL.⁸ While these materials can be engineered to fit a wide variety of applications, their properties are inherently limited. In general, these polymers are crystalline with relatively high glass transition temperatures (T_g) and crystalline melting points (T_m). As such, they are mechanically strong but can be brittle at the use temperature (37 °C). They are soluble in organic solvents, but they are hydrophobic. Due to these

properties, devices degrade on the order of months or years *in vivo*, often with a burst profile due to autocatalysis by acidic degradation byproducts.^{4, 9} Also, these polymers have no reactive functional groups along the chains, preventing the covalent binding of drugs, oligopeptides, or signaling ligands.

The incorporation of polar functional groups has been studied to expand this set of properties. Several strategies exist to functionalize the end-groups of each polyester molecule, but this survey will only be concerned with efforts to include pendant functional groups. Some of the groups that have been incorporated into aliphatic polyester repeat units are listed in Table 1.1 with their intended purposes.

Table 1.1. Structure and intended purpose of functional groups incorporated in aliphatic polyesters

Structure	Purpose(s)
carboxylic acid	water solubility; anionic group; reactive precursor to amide and ester
amine	water solubility; cationic group; reactive precursor to amide
alcohol	water solubility; reactive precursor to ester; ROP initiation site
unsaturation	crosslinking group; addition reactivity; oxidation reactivity
epoxide	polar group; nucleophilic/electrophilic reactivity
halogen	leaving group; radical reactivity
ketone	polar group; electrophilic reactivity

fluorine	polar group; surface energy modification
alkyne / azide	cycloaddition reactivity
ether	polar group

Many different types of monomer syntheses, polymer syntheses, and post-polymerization methodologies have been used to incorporate these pendant functional groups into the repeat units of polyesters. The first method is to form a protected monomer that can be polymerized and then deprotected to yield the functionalized polymer. The second strategy is to form a monomer that contains a functional group that is unreactive during the polymerization event, but that can be transmuted to a more desired functionality. Lastly, there are several examples of the direct incorporation of desired reactive functionalities using specialized polymerization techniques or post-polymerization modifications. In some cases, homopolymers that contain the desired group on each repeat unit can be formed, but often it is sufficient to form a copolymer that contains a few mole percent of the functionality or contains additional orthogonal functional groups.

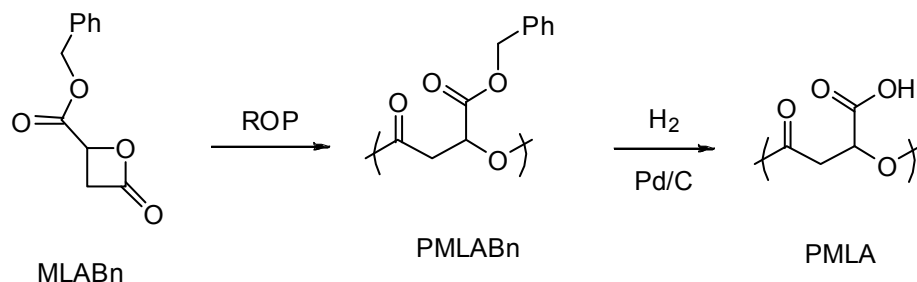
1.2 Protection-deprotection methodologies

The obvious difficulty in including reactive functional groups into polyesters is the incompatibility of some of these groups in ring-opening or step-growth polymerization reactions, which are the most commonly used routes to prepare aliphatic polyesters. Under traditional polymerization conditions, pendant alcohols, amines, and carboxylic acids will react with the monomers to yield branched or crosslinked polymers, not the desired linear functional materials. Thus, one of the most studied methodologies to incorporate functional

groups is the synthesis of a protected lactone or cyclic diester. This ring monomer can then be reacted in a ring-opening polymerization and subsequently deprotected to yield the desired polymer.

1.2.1 Incorporation of carboxylic acids

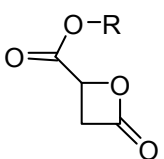
One of the first examples of a synthetic polyester containing reactive, polar functionality was the production of poly(β -malic acid) (PMLA) by Lenz and Vert in 1979.¹⁰ Their synthetic target was a carboxylate-functionalized polyester that was known to be produced in nature by several microorganisms.¹¹ In order to produce high molecular weight PMLA synthetically, a ring-opening polymerization was conducted on the benzyl ester of β -malolactone (MLABn), as depicted in Scheme 1.1. The monomer synthesis was based on bromosuccinic acid and resulted in the racemic product in three synthetic steps. After base- or acid-promoted ring-opening polymerization to form the ester-protected poly(β -malic acid) (PMLABn) and subsequent catalytic hydrogenation, the neutral polymer or carboxylate polyanion was isolated (PMLA). This polymer degraded rapidly to malic acid¹² but could be stored for long periods of time in frozen aqueous solutions.

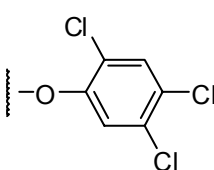


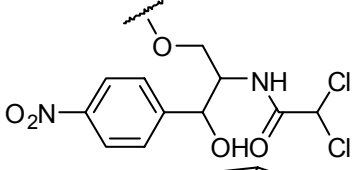
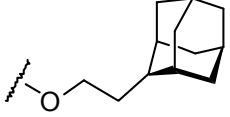
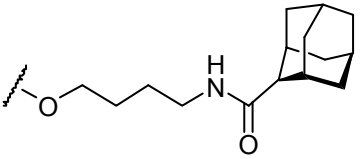
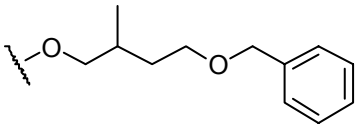
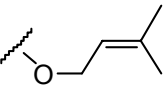
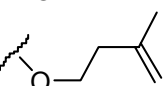
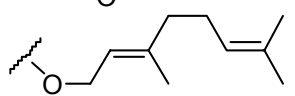
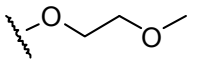
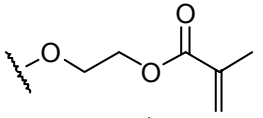
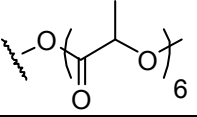
Scheme 1.1. Synthesis of poly(β -malic acid) (PMLA)

The partial deprotection of the benzyl ester led to amphiphilic structures¹³ that were later shown to be blocky in nature due to the use of heterogeneous catalysis in the deprotection step.¹⁴ Optically active polyesters were synthesized using a single isomer of aspartic acid as the starting material for the monomer synthesis.¹⁵ These studies helped to define the stereochemistry of naturally occurring PMLA, and it was observed that polymers containing either the *R* or *S* stereoisomers degraded at the same rate.¹⁶ Several studies were undertaken to increase the enantiomeric excess¹⁷ and purity¹⁸ of the MLABn monomer. By rigorously purifying each intermediate in the monomer synthesis, it was found that PMLABn could be synthesized with number-average molecular weight in excess of 1.5×10^5 g/mol (GPC in dioxane; PS standards).¹⁸ Modified monomer syntheses were designed to form other esters of malolactone which could be copolymerized with MLABn, as shown in Table 1.2. These monomers were used to form amphiphilic polymers containing strongly hydrophobic repeat units, biologically active structures, or reactive sites.

Table 1.2. Esters of malolactone studied for copolymerization with PMLABn

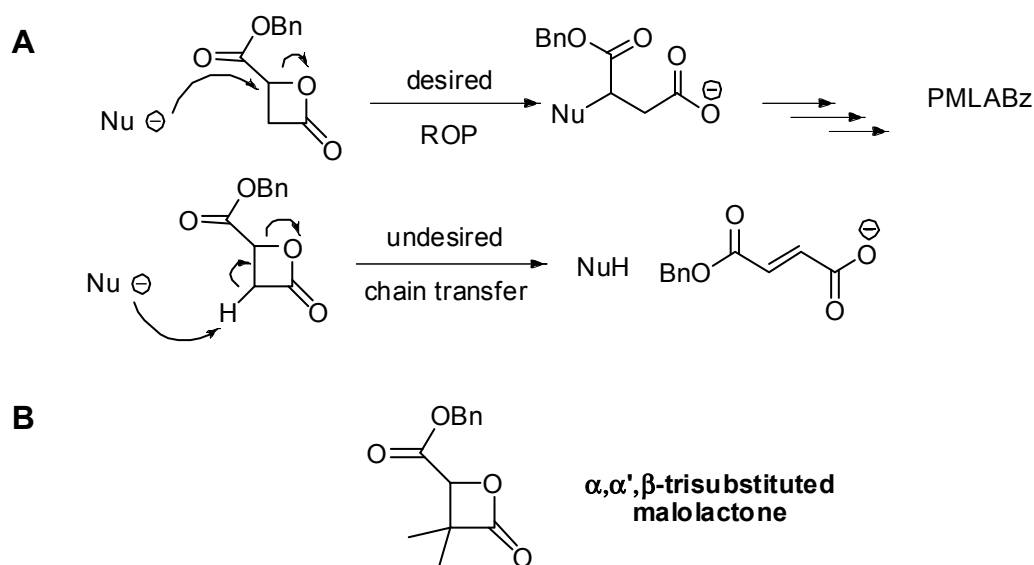


-OR	Reference	Notes
methyl ester	17	
<i>iso</i> -pentyl ester	17, 19	
	20	activating agent

	20	antibiotic
	21	
	21	
	22	biological recognition
	22	biological recognition
	22	biological recognition
	22	biological recognition
cholesteryl ester	22	biological recognition
	22	increase hydrophilicity
	22	crosslinker
	22	

Living ring-opening polymerization was also studied in PMLA systems. Barbaud hypothesized that anionic ROP conditions promoted α -hydrogen extraction and led to chain transfer in the polymerization of MLABn, as shown in Scheme 1.2 A. To circumvent this side reaction, α,α' -dimethylmalolactones were synthesized²³ and polymerized.²⁴ The success of this monomer, whose structure is shown in Scheme 1.2 B, was demonstrated under anionic conditions. MLABn was polymerized to yield a polymer with number-average

molecular weight of 7.0×10^4 g/mol and polydispersity of 1.6, while the α,α' -dimethyl MLABn was allowed to react under the same conditions and resulted in polyester with number-average molecular weight of 1.7×10^5 g/mol and molecular weight distribution of 1.1. The new lactone could also be synthesized with allyl, *sec*-butyl, and *n*-hexyl esters instead of benzyl esters. The hexyl lactone and benzyl lactones were copolymerized randomly or in sequential monomer addition reactions to form polymer micelles.^{25, 26}

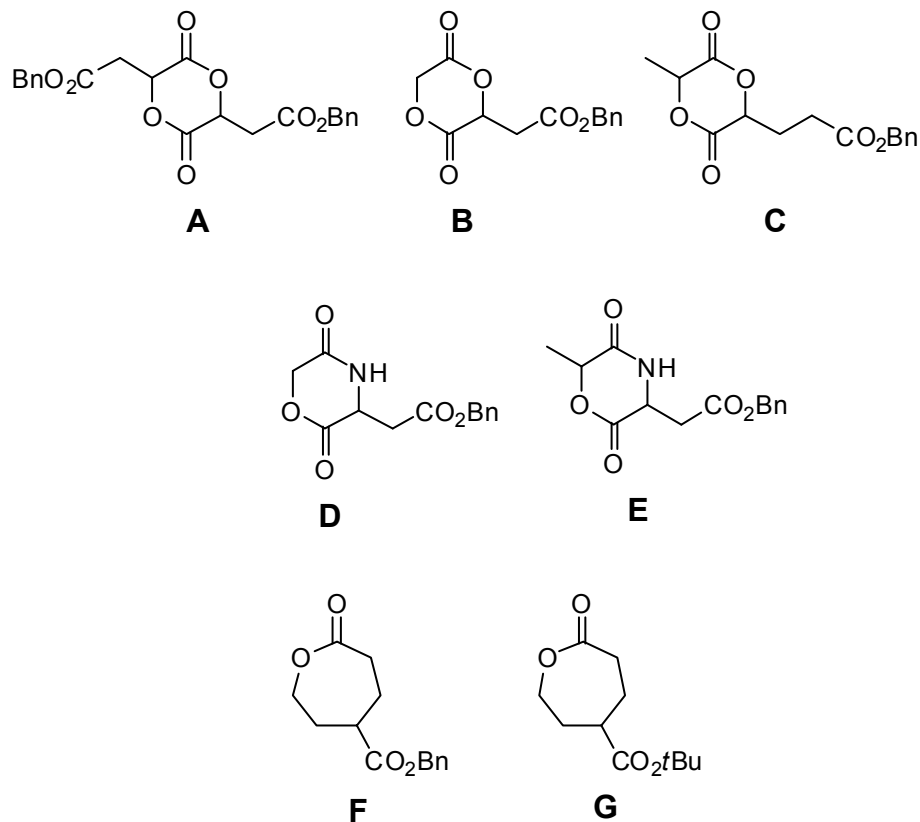


Scheme 1.2. (A) Chain transfer to monomer in PMLABn synthesis (B) Structure of α,α' -dimethyl MLABn

Protected malolactones have also been copolymerized with other lactones and lactides. Poly(β -malic acid-*co*- ϵ -caprolactone) was formed using tin octanoate catalyst and was found to have a random structure of repeat units.²⁷ It was also possible to create random copolymers of MLABn and L-lactide using the same catalyst.^{28, 29} By using an alcohol end-capped PMLABn as a macroinitiator for ϵ -caprolactone polymerization, diblock copolymers

were formed.³⁰ Mikto-arm star triblock copolymers of poly(ethylene glycol), poly(ϵ -caprolactone), and poly(benzyl malolactone) were also formed by the use of a difunctional macroinitiator.³¹

Figure 1.1. Structures of pendant ester-containing monomers



The successful synthesis of poly(β -malic acid) inspired the production of other protected carboxylic acid monomers. The formation of poly(α -malic acid) by ring-opening polymerization of a benzyl ester protected monomer (Figure 1.1 A) was reported in 1985, shortly after PMLA's initial studies were completed.³² The structural similarity of this monomer to lactide led researchers to attempt copolymerizations to produce poly(α -malic acid-*co*-lactic acid).³³ Unfortunately the reactivity of the two monomers was quite different,

resulting in copolymers whose final compositions correlated poorly to the monomer feed ratios. Other researchers attempted to create materials with fewer carboxylic acid groups by creating a monomer that would result in poly(α -malic acid-*alt*-glycolic acid).³⁴ This cyclic diester is depicted in Figure 1.1 B, and it was later copolymerized with L-lactide to form copolymers that had good feed/composition fidelity.³⁵ A later report showed the synthesis and polymerization of a glutamic acid based lactide (Figure 1.1, compound C).³⁶ This monomer was successfully incorporated into homopolymers and random copolymers with L-lactic acid.

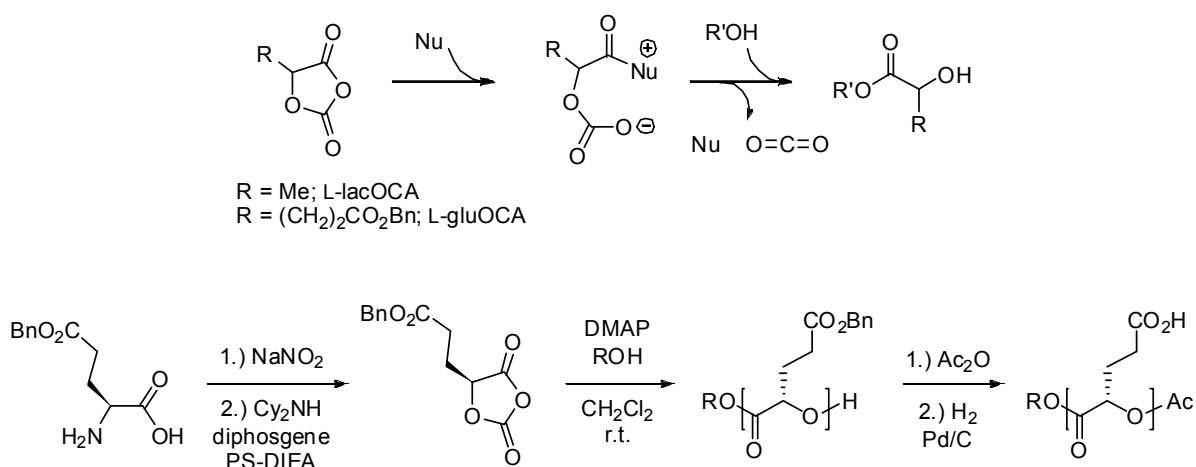
A similar strategy was employed in the synthesis of morpholine-2,5-diones derived from amino acids. The resulting polyesters from the ROP of monomers D and E in Figure 1.1 are alternating poly(ester-amides) with pendant benzyl esters.^{37, 38} The homopolymers were often isolated in low molecular weights with broad PDIs, but copolymerization with L-lactide often resulted in more controlled reactions.

In 2000, Trollsås, *et al.*, reported the synthesis of a series of functionalized ϵ -caprolactone monomers, including two that could be deprotected to yield carboxylic acid functionality (Figure 1.1 F & G).³⁹ The benzyl and *t*-butyl ester functionalized monomers were polymerized, but high molecular weight polymer was difficult to obtain. Upon deprotection of these monomers, a GPC peak shift was noted after ester cleavage, indicating degradation of the main chain as well as the side groups. However, NMR analysis indicated only minimal molecular weight loss.

While the majority of side-chain ester functionalized polyesters are derived from cyclic monomers, one example uses an interfacial step-growth polymerization to synthesize

poly(ester-amide)s that bear benzyl ester side groups.⁴⁰ Unfortunately, little characterization of the polymer was reported, and the deprotection of the polymer was not described.

Many of the protected monomers that have been discussed suffer from reduced reactivity relative to lactones, glycolide, or lactide. One exemplary monomer based on benzyl-protected glutamic acid has been reported to have very high reactivity, and was in fact slightly more reactive than its lactide counterpart (Scheme 1.3). The synthesis of *O*-carboxyanhydride activated lactic acid (L-lacOCA) allowed for the production of high molecular weight polyesters in minutes at room temperature using organic catalysts.⁴¹ The enhanced reactivity of this 5-membered ring towards opening is attributed to increased enthalpic (ring strain) and entropic (CO₂ release) driving forces. This living polymerization was then applied to a benzyl glutamate derivative of the OCA monomer.⁴² Structural studies indicated that the L-gluOCA monomer had similar ring strain to the L-lacOCA, and thus it was able to polymerize rapidly to high molecular weight ($\langle M_n \rangle$ 1.8 x 10⁴ g/mol; PDI 1.18; 90 mins). Block and random copolymers were also synthesized. Kinetic studies of copolymerizations indicated that the consumption of L-gluOCA was only slightly faster than L-lacOCA, allowing for clean incorporation of desired amounts of each repeat unit at any monomer ratio. Lastly, after acetate end-capping of the terminal alcohol, quantitative reduction of the benzyl esters to the acid did not result in any molecular weight loss.



Scheme 1.3. (A) Mechanism of OCA ring-opening polymerization (B) Synthesis of L-gluOCA and poly(glutamic acid ester)

1.2.2 Incorporation of amines

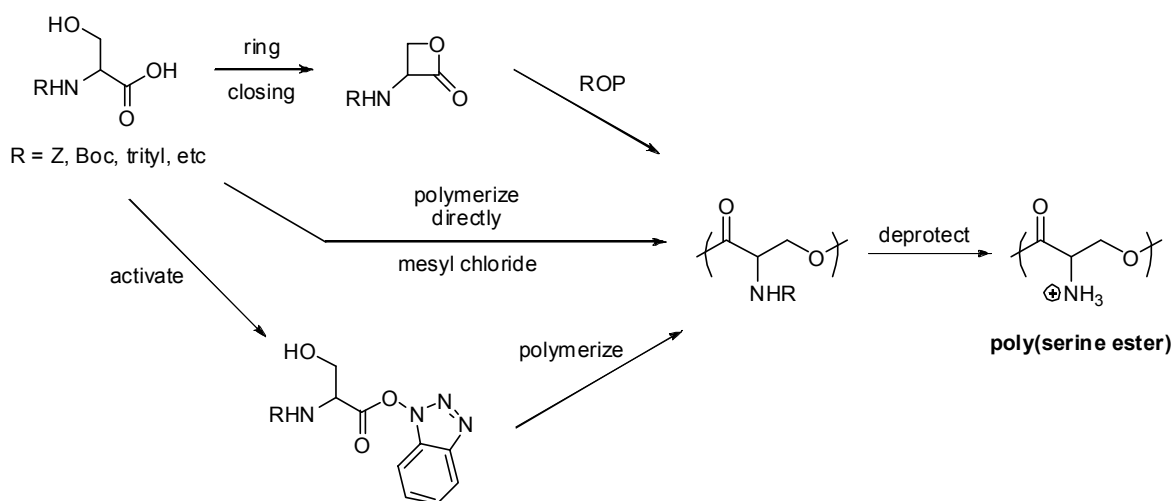
The protection-deprotection strategy was also applied to the synthesis of polyesters with pendant amine functionality. In 1990, the first publication of this sort reported the synthesis of a serine-based lactone whose amines were protected with benzyloxycarbonyl (Z) groups.⁴³ This monomer was polymerized using tetraethylammonium benzoate as initiator to yield polymer with a number-average molecular weight near 9.0×10^3 g/mol. The low molecular weights were attributed to chain transfer, while the use of a *tert*-butoxycarbonyl (Boc) protecting group helped decrease the side reaction. The resulting poly(serine ester) was isolated after acidic deprotection or catalytic hydrogenation, although chromatographic molecular weight determination proved difficult due to poor organic solubility.

Another report in the same year demonstrated the synthesis of a trityl-protected amine-containing malolactone derived from serine.⁴⁴ This monomer was isolated in only 10 % yield, but could be polymerized using tetrabutylammonium acetate to a number-average

molecular weight of 3.0×10^4 g/mol. After deprotection, however, the molecular weight fell to 6.5×10^3 g/mol, with an increased PDI, indicating ester cleavage.

In 1992, poly(serine ester) was again synthesized, but this time from the step-growth polymerization of an activated ester of *N*-protected serine.⁴⁵ First, serine was protected with Z, Boc, *p*-methoxybenzylcarbonyl or *p*-nitrobenzylcarbonyl groups. Then the ester was activated with 1-hydroxybenzotriazole using carbodiimide coupling. The yield of this step was 90 %, a considerable advantage over the synthesis of lactone monomers that allowed access to the same polymer repeat unit. Finally, the bulk polymerization of the activated esters yielded protected polyesters with number-average molecular weights up to 2.0×10^4 g/mol with narrow polydispersity (PDI < 1.5).

Another step-growth methodology for the synthesis of poly(serine ester) relied on monomer activation with methanesulfonyl chloride.⁴⁶ The *N*-Z-protected serine was reacted in one step at room temperature to yield high molecular weight polyesters ($\langle M_w \rangle 3.0 \times 10^4$ g/mol). Deprotection to yield the primary amine proceeded to high conversion, but resulted in a 15 % decrease in molecular weight. This was considered a modest concession given that the polymer synthesis was possible on larger scales than with ROP strategies. The methods used for the synthesis of poly(serine ester)s are summarized in Scheme 1.4.

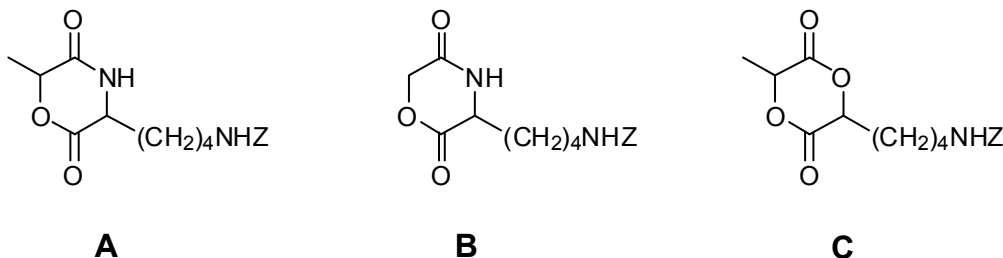


Scheme 1.4. ROP and step-growth routes to poly(serine ester)s

Langer, *et al.*, also reported the synthesis of amine-bearing polyesters, but their methodology relied on incorporation of lysine repeat units.⁴⁷ A Z-protected amine-containing morpholine-2,5-dione was synthesized in 4 steps (Figure 1.2 A). It was copolymerized with L-lactide using a tin(II) catalyst to yield a polymer with number-average molecular weight of 4.5×10^4 g/mol and PDI of 1.4. This polyester had only 1.3 mole percent of protected lysine repeat units, and could be only partially deprotected without considerable degradation. Despite the small amount of amine groups incorporated into the polyesters, the final polymer exhibited accelerated hydrolytic degradation due to increased hydrophilicity. The amine groups were also used to graft oligopeptides (GRGDY) that promoted cell adhesion to the polyesters. In a subsequent report, the same authors were able to increase the molecular weights of the polyesters as well as the amount of lysine repeat units that could be incorporated.⁴⁸ By increasing the feed ratio to 30%, they observed about 10% incorporation of the new monomer into the polyester, but the polymer was isolated in only 20 % yield. By increasing the polymerization time and decreasing the temperature, a

polymer with a weight-average molecular weight of 9.5×10^4 g/mol and 2.4 mole % of the protected lysine repeat unit was isolated. This synthetic improvement allowed for further studies of the degradation behavior of these materials.

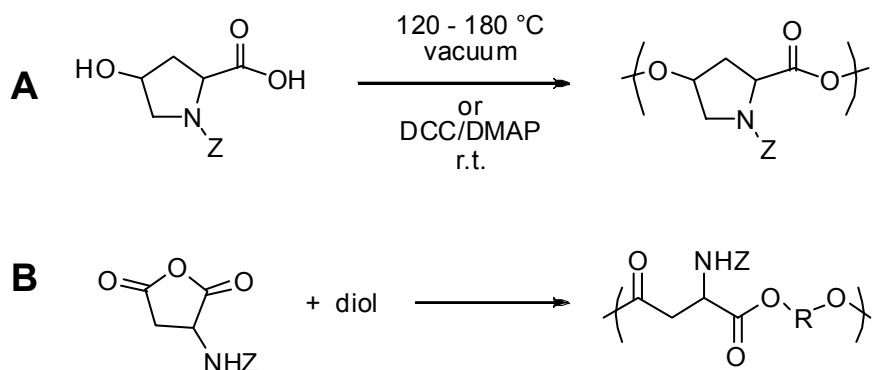
Figure 1.2. Functionalized monomers derived from lysine



A similar strategy was employed by Ouchi, *et al.*, but the resulting repeat unit was poly(lysine-*alt*-glycolide) instead of poly(lysine-*alt*-lactide). The monomer shown in Figure 1.2 B was copolymerized with L-lactic acid to yield polymers of modest molecular weights ($\langle M_n \rangle$ $3 - 10 \times 10^3$ g/mol), but no degradation was observed after deprotection using HBr/acetic acid to remove the benzyloxycarbonyl groups.⁴⁹ Further reports detailed the synthesis of diblock copolymers of the *N*-protected morpholine-2,5-dione and L-lactide.⁵⁰

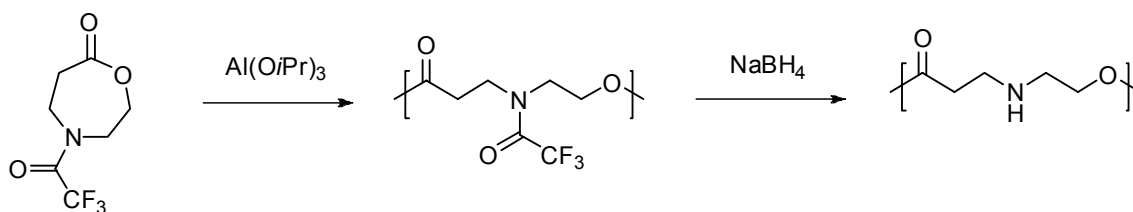
A similar monomer (Figure 1.2 C) was synthesized and polymerized by Weck, *et al.* This cyclic diester bore a Z-protected lysine side chain and could be homopolymerized or copolymerized with L-lactic acid.³⁶ In the case of the homopolymer, a fairly low number-average molecular weight was observed by GPC (8.0×10^3 g/mol; PDI 1.4). Copolymers had a predictable composition based on the feed and were isolated in higher molecular weights (2.4×10^4 g/mol; PDI 2.1).

A few step-growth polymerizations have employed the amine protection-deprotection strategy as well. The first example is based on a monomer derived from hydroxyproline, an uncommon amino acid.⁵¹ After Z-protection of the amine, a high temperature AB step-growth polymerization, shown in Scheme 1.5 A, gave the protected polyester in relatively low molecular weight ($\langle M_n \rangle$ 5.3×10^3 g/mol; PDI 1.7; GPC). Deprotection yielded a polymer with a similar molecular weight (M_p 4.6×10^3 g/mol; MALDI-TOF). To determine the extent of degradation in the deprotection step chromatographically, the polymer was protected again and subjected to subsequent GPC analysis. The results were similar ($\langle M_n \rangle$ 6.6×10^3 g/mol; PDI 1.3), and the difference in the results was attributed to fractionation of the polymer during the work-up. This amine-containing polymer degraded very quickly to a natural product, and was used to study the delivery of DNA. A second study of this polymerization yielded higher molecular weights at room temperature by using 200 mole % of *N,N'*-dicyclohexylcarbodiimide (DCC) as a coupling agent.⁵² The protected polymer had a weight-average molecular weight of 7.9×10^3 g/mol.



Scheme 1.5. Use of step-growth chemistry to synthesize *N*-protected polyesters

The second step-growth polymerization of *N*-protected monomers was an AA-BB reaction of *N*-Z-aspartic anhydride and 1,4-cyclohexanedimethanol.⁵³ Protected aspartic acid was allowed to react with excess acetic anhydride to yield the desired amine-containing monomer (Scheme 1.5 B). Upon acid-catalyzed polycondensation with the diol, polymers with moderate molecular weights were isolated ($\langle M_w \rangle$ 1 – 5 x 10³ g/mol). To increase the molecular weight and hydrophilicity of the final material, poly(ethylene glycol)s with different molecular weights were also condensed with the protected anhydride.⁵⁴

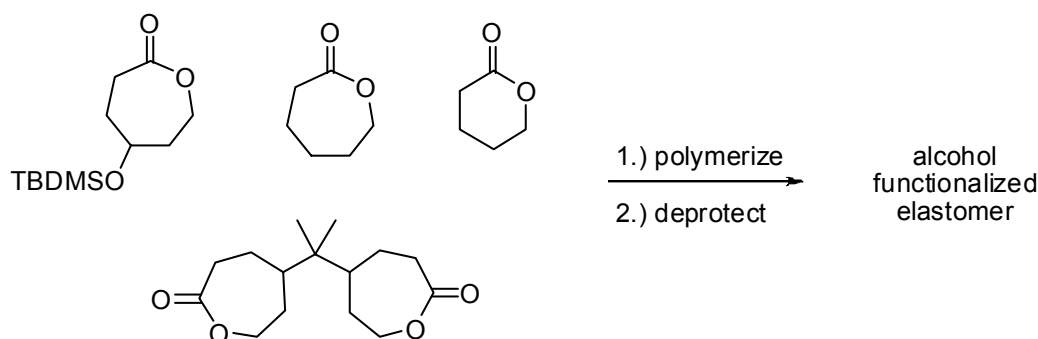


Scheme 1.6. Amine-containing ϵ -caprolactone polymerization and deprotection

Trollsås, *et al.*, synthesized an amine-containing ϵ -caprolactone derivative for use in ring-opening polymerization, as shown in Scheme 1.6.³⁹ The homopolymer was formed in high molecular weights ($\langle M_n \rangle$ 1.5 x 10⁴ g/mol; PDI 1.35), and copolymers with ϵ CL also could be synthesized. The deprotection of this polymer was somewhat difficult; the quantitative cleavage of all of the amide groups came at the expense of some ester cleavage. Higher molecular weight polyesters could be isolated at lower conversions of the deprotection reaction.

1.2.3 Incorporation of alcohols

In spite of the success of the previous strategies and the wide scope of known alcohol protecting groups, the first synthesis to apply this methodology to prepare alcohol-functionalized polyesters did not occur until the late 1980's, with very few publications following until the late 1990's. This may be attributed to the fact that deprotection conditions required for most alcohol protecting groups require fluorinated reagents, acids, or bases, all of which degrade polyesters. Pitt, *et al.*, reported the synthesis of γ -*tert*-butyldimethylsiloxy- ϵ -caprolactone and its copolymerization with ϵ -caprolactone, δ -valerolactone, and a diester crosslinker monomer (Scheme 1.7).⁵⁵ The desired elastomers were deprotected using acetic acid, but the removal of the silyl ether groups also led to a drastic decrease in the modulus of the material. In one example, 70 % conversion of the TBDMS deprotection led to a decrease in modulus from 1.62 MPa to 0.56 MPa.



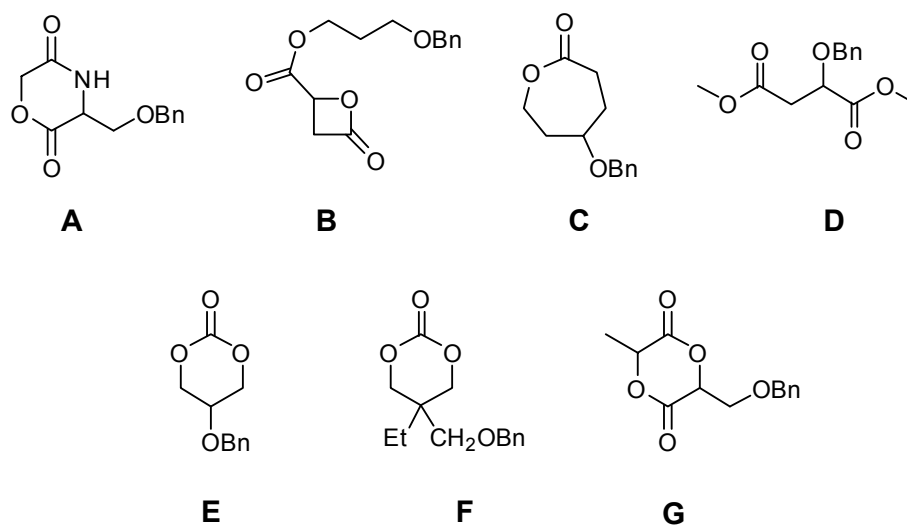
Scheme 1.7. Synthesis of alcohol functionalized elastomers via silyl ether protecting groups

More recent reports detailed the synthesis, polymerization, and deprotection of γ -triethylsiloxy- ϵ -caprolactone.^{56, 57} In the first report, copolymers of the protected monomer with ϵ CL yielded a polyester that was deprotected with hydrofluoric acid. The reaction

degraded the polymers, but if the deprotection was conducted using 2 % HF in acetonitrile for only 30 minutes at 20 °C, polymer with 23 mol % of alcohol (82 % conversion from ether to alcohol) was isolated with 6 % molecular weight loss. In the second example, the revealed alcohol groups were used to form ester bonds with carboxylic acid-terminated poly(ethylene glycol)s, resulting in graft copolymers.

Considering the success of the benzyl ester as a protecting group for carboxylic acids, John *et al.*, first used benzyl ethers to mask hydroxyl functionality.⁵⁸ The morpholine-2,5-dione synthesis began with benzyl-protected serine and afforded the cyclic monomer in only two steps. The polymerization of this monomer, whose structure is shown in Figure 1.3 A, resulted in the benzyl ether functionalized polyester. Upon hydrolytic cleavage (H_2 ; Pd/C), alcohol functionality was revealed. A subsequent step provided polyesters with pendant crosslinkable groups by reaction with acryloyl chloride. The protected monomer could be copolymerized with ϵ CL⁵⁹ or LLA⁶⁰ to result in crosslinked networks.

Figure 1.3. Benzyl-protected monomers used as precursors to alcohol functionalized polyesters



Another synthesis that took advantage of the benzyl protecting group was reported for an analogue of MLABn.⁶¹ In this case, the side-chain ester was terminated with a benzyl group that would reveal the desired alcohol functionality. This polymer was studied as a neutrally charged analogue for PMLA. After ring-opening the monomer (Figure 1.3 B) for 15 days, polymer with a number-average molecular weight of 4.7×10^3 g/mol was isolated. After deprotection, a water-soluble polyester was isolated with the same molecular weight. The copolymerization of this monomer was also studied with a few of the malolactone monomers shown in Table 1.2.

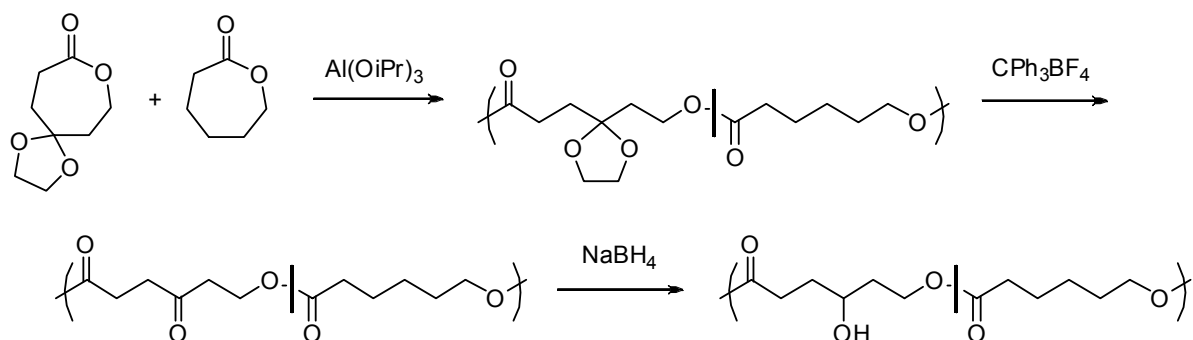
Another poly(γ -hydroxy- ϵ -caprolactone) synthesis was reported using benzyl protection, rather than the previous silyl ether.³⁹ The monomer, shown in Figure 1.3 C, was polymerized and then deprotected using the traditional hydrogenation conditions. Unfortunately, these conditions led to a significant decrease in the molecular weight of the polyesters.

A step-growth polymerization exhibited the efficient polymerization of a protected alcohol containing diester.⁶² Monomer D in Figure 1.3 was copolymerized with dimethyl succinate and 1,4-butanediol to yield high molecular weight polyesters ($\langle M_n \rangle$ $1.5 - 3.1 \times 10^4$ g/mol) with high dispersities (PDI 4.4 – 6.4). After deprotection, malic acid-based repeat units were revealed, but at the expense the molecular weight of the original polyesters.

Another step-growth polymerization was used to form alcohol-functionalized poly(ester carbonate)s.⁶³ First succinic acid and excess 1,4-butanediol were condensed to make polyester diols. These polyols were then used as macroinitiators for ROP of monomers E and F from Figure 1.3 to form benzyl protected triblock copolymers. Unfortunately, as the deprotection reaction proceeded, molecular weight loss was observed.

A final example of benzyl protected polyesters was shown in 2006 by Gerhardt.³⁶ In this report, a functionalized lactide (Figure 1.3 G) was homopolymerized or copolymerized with LLA. The resulting polymers were similar to previously described poly(*serine-alt-lactide*)s, but in this case it was easier to include higher quantities of the alcohol functionality while still maintaining high molecular weights.

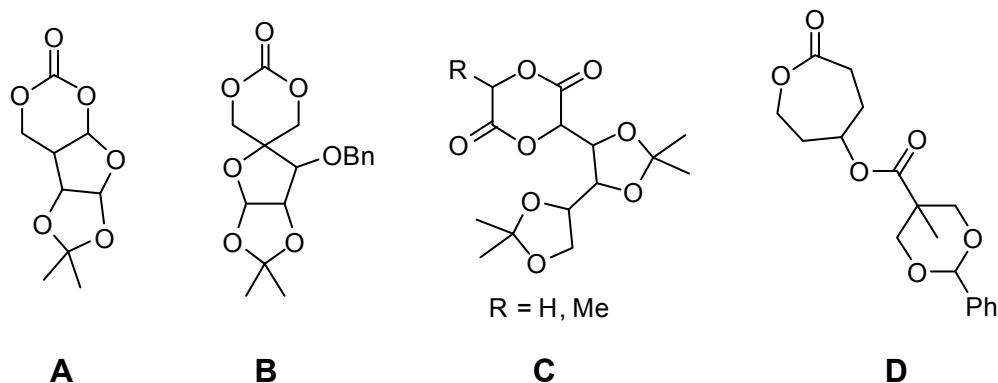
While the silyl and benzyl ether protecting groups seemed promising, a more successful protection-deprotection strategy was realized in ketal- and acetal-based methodologies. Tian, *et al.*, first reported the synthesis of the acetal-functionalized lactone, 1,4,9-trioxaspiro[4.6]-9-undecanone (TOSUO) that could be homopolymerized or copolymerized with ϵ CL.⁶⁴ Subsequent reports detailed the conversion of the acetal group to a ketone using trityl boron tetrafluoride and the reduction of the ketone group to the alcohol using sodium borohydride.⁶⁵ These reactions are depicted in Scheme 1.8. Gel permeation chromatograms of each of the resultant polymers showed a shift towards longer retention times after each step, indicating possible hydrolytic degradation. In a later report, block copolymers were formed that contained PCL and acetal-containing blocks.⁶⁶ The same set of post-polymerization reactions were performed, and GPC chromatograms of these polymers displayed no shift in retention times after the deprotection and reduction steps.



Scheme 1.8. Polymerization of TOSUO and subsequent post-polymerization reactions to reveal alcohol functionality

The same strategy was employed for the formation of polyester-grafted dendrimers.⁶⁷ The use of multifunctional initiators ($f = 2, 4$, or 8) in the copolymerization of TOSUO and ϵ CL allowed the formation of multiarm star copolymers. Upon conversion of the acetals to alcohols, the macromolecule was used as a multifunctional initiator to form densely grafted dendrimeric polyesters. Another application of the TOSUO monomer was described in the copolymerization with γ -triethylsiloxy- ϵ -caprolactone and ϵ CL.⁶⁸ The use of these orthogonal protecting groups allowed for selective deprotection of only part of the alcohol groups, leaving others available for later reactions.

Figure 1.4. Ketal- and acetal-functionalized carbonate and lactone monomers



The synthesis of isopropylidene-protected monomers was also reported. Chen and Gross synthesized monomer A in Figure 1.4, which was successfully copolymerized with LLA to form poly(ester carbonate)s.⁶⁹ These polymers were obtained in very high molecular weights ($\langle M_n \rangle$ 7.8×10^4 g/mol; PDI 1.9; 7 mol % A). Upon cleavage of the ketal with trifluoroacetic acid, the alcohol-functionalized copolymer could be isolated. Unfortunately, these conditions degraded the backbone of the poly(ester carbonate), and only partial deprotection was possible. Another example from the same group described the synthesis of a carbonate monomer with orthogonal ketal and benzyl ether protecting groups.⁷⁰ This monomer (B in Figure 1.4) behaved similar to compound A in copolymerizations with lactide, but deprotection of one or both of the protecting groups was possible without substantial molecular weight loss.

The syntheses of the cyclic diesters in Figure 1.4 C were based on partially protected gluconic acid, and each monomer bore two ketal protecting groups.^{71, 72} The glycolide- and lactide-based forms of this monomer were synthesized and polymerized, although the glycolide form (R = H) was more successful. Homopolymers could be synthesized to high molecular weight ($\langle M_w \rangle$ 3.2×10^4 g/mol), although copolymers with LLA allowed for larger

macromolecules. It was noted that the deprotection conditions (acetic acid/water/acetone or iodine/acetone/methanol) tended to degrade the polyester backbone while only liberating a fraction of the 1,2-diols. Even still, this polymer was successfully coupled with naphthoyl chloride to form a fluorescently labeled polyester.⁷³

An acetal-based ϵ -caprolactone (Figure 1.4 D) was synthesized in an effort to improve the previous synthesis of hydroxy-functionalized PCL.³⁹ Removal of the benzylidene protecting group in a single post-polymerization step revealed a 1,3-diol, rather than a single hydroxyl group. Also, the primary alcohols were expected to be more reactive than the secondary alcohols that had been incorporated previously. The homopolymer was synthesized to fairly high molecular weight ($\langle M_n \rangle$ 1.2×10^4 g/mol; PDI 1.4), and NMR analysis revealed no degradation after deprotection via catalytic hydrogenolysis.

Taken as a whole, the protection-deprotection strategies have been successfully explored for the inclusion of reactive functionality in polyester repeat units. Examples of carboxylic acids, amines, and alcohols from ring-opening and step-growth polymerizations have been described. However, some practical considerations of this strategy are that the synthesis of a protected monomer can be synthetically challenging and the purity of the final monomer product is of utmost importance. Also, the low reactivity of these monomers in copolymerization reactions with ϵ CL or LLA often makes targeted compositions difficult to achieve accurately. Perhaps the most detrimental aspect of this strategy is the requisite post-polymerization deprotection step. Many of the deprotection reactions lack selectivity in the cleavage of the required pendant ester, amide, or ether. Cleavage of the main chain esters and resulting molecular weight loss can sometimes be avoided, but this side reaction is accepted as a necessary consideration for this methodology.

1.3 Functional group transformation methodologies

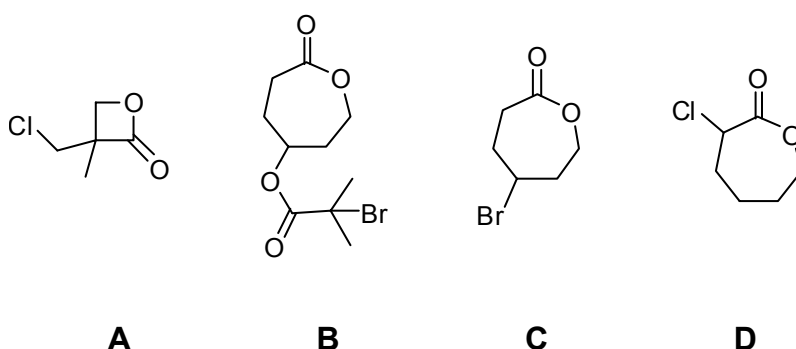
Given these aspects of the protection-deprotection methodology, other strategies have been explored that allow simpler monomer syntheses and milder post-polymerization reactions. The next approach relies on the design of monomers whose functional groups are orthogonal to esterification reactions. The key criteria of this approach are that the chosen functional group does not interfere in the polymerization reaction, that the functional group can be transformed into a useful moiety in post-polymerization reactions, and that the conditions of the subsequent reactions do not detrimentally affect the ester bonds of the backbone. Key monomer structures that allow for functional aliphatic polyesters by this methodology include halogens, azides, double bonds, triple bonds and ketones. These groups are unreactive in most ring-opening and step-growth polymerization conditions, but they can be usefully transformed afterwards. The utility of a bromine or chlorine atom as a leaving group for substitution and elimination reactions is immediately obvious, and recent advances in atom transfer radical reactions^{74, 75} also make the functionality attractive. Unsaturated polyesters can participate in a wide range of addition reactions and can be oxidized to epoxides, alcohols, diols, and carboxylic acids. Azide- and alkyne-bearing polyesters capable of cycloadditions have also been synthesized. Ketone-bearing polyesters have been described in Section 1.2.3, but methodologically distinct post-polymerization addition reactions result in grafted polyesters.

1.3.1 Halogen transformations

Halogens were the first functional groups of this type that were explored in monomer and polymer synthesis. The first report of a chlorine-containing aliphatic polyester came in

1999, and was based on a chlorine functionalized propiolactone, shown in Figure 1.5 A.⁷⁶ A highly crystalline homopolymer was isolated, and copolymers with ϵ CL were also produced.⁷⁷ The subsequent substitution of the primary halide with pyridine was reported to reduce the molecular weight by about 25 %, but this transformation allowed for a more hydrophilic polyester.

Figure 1.5. Halogen-containing lactone monomers



The first bromine-functionalized aliphatic polyester was a ϵ CL based monomer that featured a pendant α -bromopropionate as an atom transfer radical polymerization (ATRP) initiation site.⁷⁸ This monomer (Figure 1.5 B) was used to synthesize brush copolymers of PCL and PMMA through three distinct synthetic routes. First, the monomer was copolymerized with ϵ CL, and the subsequent multifunctional macroinitiator was used for the ATRP of methyl methacrylate. Conversely, the new monomer could initiate ATRP first, and then these lactone end-capped MMA macromonomers were incorporated into copolymers with ϵ CL. It was also demonstrated that this molecule could simultaneously function as a monomer and initiator in a tandem ATRP/ROP reaction to yield brush copolymers. A later report showed several iterations of these polymerization reactions using HEMA as a

complementary ATRP monomer and ROP initiation site.⁷⁹ Linear copolymers with ϵ CL were subjected to substitution with pyridine or elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU). In substitution reactions, the resulting quaternary amine-containing polyesters suffered molecular weight loss due to nucleophilic side reactions with the ester groups. After dehydrohalogenation, the resulting acrylate-functionalized polyesters became precursors to crosslinked polyesters.⁸⁰

A similar monomer, γ -bromo- ϵ -caprolactone (Figure 1.5 C) was synthesized and studied in living polymerization reactions.⁸¹ The homopolymer could be formed in relatively high molecular weights ($\langle M_n \rangle$ 1.6×10^4 g/mol; PDI 1.15), or higher molecular weight macromolecules could be produced in copolymerization reactions with ϵ CL. The living nature of these ROP reactions was demonstrated by the use of sequential monomer addition to produce diblock copolymers. Moreover, the resulting polymers were exposed to the previously discussed post-polymerization reactions with greater success.⁸⁰ The pyridine substitution could be conducted at lower temperatures, preventing molecular weight loss. The dehydrohalogenation of this polyester led to three isomeric repeat units with double bonds in the α , β or γ positions. Further manipulations of these unsaturated polyesters are discussed in Section 1.3.2.

The reactivity of α -halogens was exploited in studies on α -chloro- ϵ -caprolactone (Figure 1.5 D).⁸² The monomer was easily synthesized and incorporated into homopolymers, as well as random and block copolymers with ϵ CL. The repeat unit of the polymer had the proper structure to act as a site for atom transfer radical reactions, such as living polymerization or vinyl addition (ATRA). The ATRP of MMA was completed to create brush copolymers, while ATRA was used to graft 3-butenyl benzoate. Further studies on the

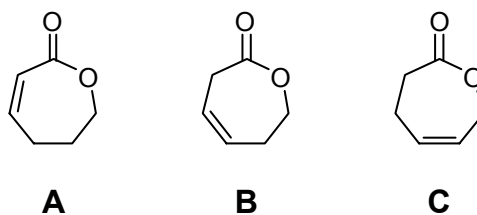
scope of the ATRA reaction revealed that the success of the reaction depended greatly on the structure of the substrate.⁸³ The grafting of unsaturated carboxylic acids, epoxides, or alcohols often required extended reaction times to proceed to moderate conversion. These conditions resulted in the degradation of the polyester when 3-buten-1-ol was used as the ATRA substrate. Despite this limitation, this strategy was later employed to form heterograft copolymers.⁸⁴ The chlorine-bearing polyester was first used to graft allylic poly(ethylene glycol), and then the remaining halogens were used to initiate the ATRP of styrene.

A final application of α -chloro- ϵ -caprolactone was in the synthesis of azide-containing polyesters. The lactone was copolymerized with ϵ CL, and subsequent sodium azide substitution yielded the desired polyester.⁸⁵ A complementary azide-functionalized monomer strategy was also successful, but long reaction times in the substitution reaction of the lactone made this approach less practical. The resultant azide-containing polyester was subjected to the copper(I)-catalyzed azide-alkyne cycloaddition (click reaction) to create grafted polyesters. A wide variety of functional groups were initially appended to the polyester, including benzoate esters, tertiary amines, quaternary amines, and poly(ethylene glycol)s. A later report showed a wider scope of alkyne coupling partners, including alcohols, acrylates, and α -bromopropionates.⁸⁶ The synthesis of poly(α -chloro- ϵ -caprolactone) was successful, but conversion to the corresponding azide-containing homopolymer was compromised by partial degradation of the polyester during the nucleophilic substitution reaction. Also, partial degradation was noted in attempts to graft various alcohol-containing alkynes. The flexibility of the click strategy was demonstrated in the synthesis of PCL/PEO copolymers with “tadpole” architectures.⁸⁷

1.3.2 Unsaturation transformations

As was previously discussed, unsaturated repeat units of PCL could be obtained by the dehydrohalogenation of poly(γ -bromo- ϵ -caprolactone). This led researchers to study the synthesis of unsaturated lactones and their polymerizations.⁸⁰ The mixture of α -, β -, and γ -unsaturated ϵ -caprolactones (Figure 1.6) was synthesized and polymerized. The degree of reactivity in the polymerization reaction was found to be $B > C > A$. The chromatographic purification of A was possible, but efforts to separate B and C were unsuccessful. The resultant unsaturated copolymers were oxidized with 3-chloroperbenzoic acid to yield epoxidized polyesters. The acrylic type repeat units that resulted from the incorporation of monomer A were unable to participate in this reaction due to the electron withdrawing character of the ester group.

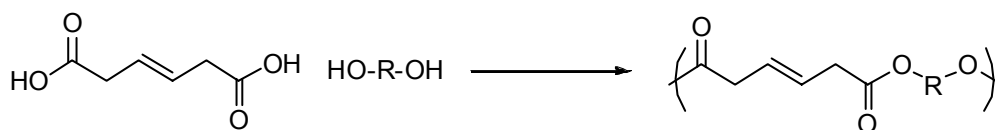
Figure 1.6. Unsaturated lactones leading to double bonds in the main chain of resultant polyesters



A subsequent report gave more detail on the properties of monomers A and its copolymerization into random or block copolymers with ϵ CL.⁸⁸ In order to isolate monomer B exclusively, α -chloro- ϵ -caprolactone was synthesized and exposed to elimination conditions to yield a mixture of only monomers A and B.⁸⁹ The successful separation of lactone B from lactone A allowed for the controlled synthesis of unsaturated polyesters

whose double bonds were not in conjugation with the carbonyl group. This polyester was oxidized to the epoxide, as had been previously demonstrated. Further functionalization of the polymer was possible by nucleophilic ring-opening of the epoxide. The use of a mild thiol nucleophile ensured that degradation of the polyester backbone would not occur. The double bond in lactone B was also exploited to form ester-containing copolymers by ring-opening metathesis polymerization (*vide infra*).⁹⁰

A step-growth polymerization allowed for the synthesis of similar unsaturated polyesters from commercially available monomers.⁹¹ Polycondensation of *trans*- β -hydromuconic acid (HMA) with a diol resulted in linear polyesters whose thermal properties could be varied by the choice of diol, as shown in Scheme 1.9. The unsaturation in these polyesters could similarly be oxidized to the epoxide, but no subsequent reaction was reported. Radical curing reactions were reported for liquid, amorphous prepolymers formed from HMA and ether-containing diols.⁹²

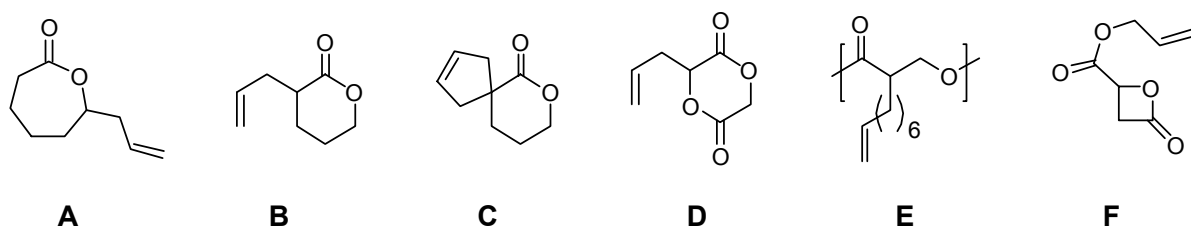


Scheme 1.9. Step-growth polymerization of unsaturated polyesters

Several lactones that contain unsaturated side chains have also been synthesized and polymerized. Initial reports investigated allylic lactones, as shown in Figure 1.7. Oxidation of 2-allyl cyclohexanone with mCPBA yielded compound A, ϵ -allyl- ϵ -caprolactone, in one step. After the lactone was separated from epoxidized byproduct, it was incorporated into homopolymers or copolymers with ϵ CL.⁹³ The resulting unsaturated polyesters were

functionalized by bromination, epoxidation, or hydrosilylation to yield polar, reactive polyesters.

Figure 1.7. Allylic lactones and their derivatives



An analogous compound, α -allyl- δ -valerolactone (Figure 1.7 B), was also synthesized.⁹⁴ This monomer was synthesized cleanly by reaction of the lithium enolate of δ -valerolactone with allyl bromide. The monomer was subsequently incorporated into homopolymers or copolymers with ϵ CL or δ VL. The allyl group was oxidized to the 1,2-diol, and immediate GPC analysis indicated that the post-polymerization reaction did not degrade the polyester backbone. However, the shelf life of the alcohol-functionalized polyester was short; daily GPC analysis of the resultant polyester revealed steady molecular weight loss that depended on the alcohol content. A slight modification to the synthesis allowed for a more stable repeat unit that performed much more effectively.⁹⁵ The reaction of δ -valerolactone with allyl bromide in two sequential reactions allowed for the production of α,α' -diallyl- δ -valerolactone. Dilute reaction conditions allowed ring-closing metathesis (RCM) of this compound to produce the desired cyclopentene-functionalized lactone (Figure 1.7 C). This monomer was copolymerized with ϵ CL and oxidized to the 1,2-diol. Again, the oxidation conditions were mild enough that no polyester molecular weight loss was observed. In this polyester repeat unit, the two secondary alcohols are confined by the ring.

Since they are less reactive, there was no degradation as was previously observed. The resultant polyester was coupled to carboxylic acid-terminated poly(ethylene glycol)s, allowing formation of a hydrophilic graft copolymer.

In order to synthesize an unsaturated polyester that degrades to absorbable byproducts, an allyl-functionalized glycolide monomer (Figure 1.7 D) was prepared.⁹⁶ The copolymerization of this compound with LLA resulted in unsaturated polyesters that were oxidized in subsequent steps. In one case, the allyl group was reacted with mCPBA to prepare epoxide functionalized materials without degradation of the polyester backbone. In a second attempt, the polyester was oxidized with OsO₄ to the diol, but the group reported degradation of the polyester during the reaction or the work up. This observation is attributed to the idea that lactide or glycolide-type backbones are more susceptible to degradation during post-polymerization reactions than δ VL- or ϵ CL- type repeat units.

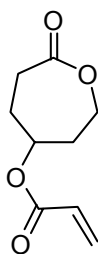
Poly(hydroxyalkanoate)s with unsaturated side chains have been obtained either from natural fermentation or chemical synthesis. Polymers containing repeat unit E in Figure 1.7 were synthesized by microbial fermentation of undecenoic acid. Once in hand, these high molecular weight polyesters were studied in post-polymerization reactions. The first example was the oxidation of the double bond to a carboxylic acid using OsO₄ and Oxone®.⁹⁷ Quantitative conversion was observed with only a slight decrease in the number average molecular weight. Another oxidation was undertaken using the hydroboration reaction.⁹⁸ While each unsaturation was converted to a primary alcohol group, chromatographic analysis of the final product was not possible.

Several unsaturated malolactones have been synthesized (Table 1.2) and polymerized. One of these, shown in Figure 1.7 F, was reacted in the radical addition of mercaptoethanol.⁹⁹

The resultant alcohol-functionalized polyester was used as a multifunctional macroinitiator for the ROP of ϵ CL to form brush copolymers.

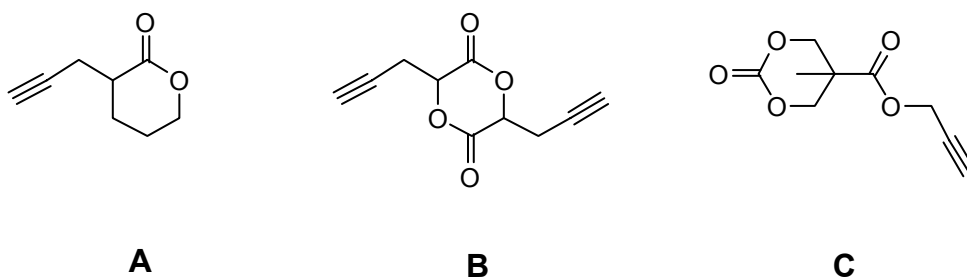
More reactive double bonds were incorporated by synthesizing acrylate-functionalized polyesters, as described by Mecerreyes, *et al.*, in 2000.¹⁰⁰ The structure of the monomer used in these studies, γ -acryloyloxy- ϵ -caprolactone, is shown in Figure 1.8. Initial studies of ATRP and ROP living polymerizations of this monomer demonstrated the utility of this compound's orthogonal reactivities. Crosslinking of copolyesters containing the pendant acrylate groups in radical reactions was successful in forming both bulk materials and intramolecularly crosslinked particles.¹⁰¹ PCL copolymers with pendant acrylate groups were also grafted onto metallic surfaces by an electrochemically initiated crosslinking reaction.¹⁰² Detailed mechanistic investigations revealed that the two ester groups of the monomer compete in ROP catalyzed by aluminum isopropoxide,¹⁰³ yet the utility of these polyesters was demonstrated repeatedly. For example, the acrylate groups are strongly reactive to Michael additions by thiols under very mild conditions.¹⁰⁴ This monomer was also used to create advanced polymer architectures via intramolecular crosslinking.^{57, 87}

Figure 1.8. Structure of γ -acryloyloxy- ϵ -caprolactone



While all of the previous examples of unsaturated polyesters have focused on double bond containing polymers, there are two examples of propargyl-functionalized polyesters. The first such report came from Emrick, *et al.*, in 2005.¹⁰⁵ The monomer, α -propargyl- δ -valerolactone, is similar to the group's previously described allylic compounds (Figure 1.9 A). This monomer is of interest because of the ability of the propargyl group to participate in mild [3+2] cycloaddition reactions with azides. The homopolymer of A and copolymers with ϵ CL were formed. The subsequent coupling of these alkyne-containing polyesters with azide-terminated poly(ethylene glycol) and GRGDS oligopeptide sequences allowed for water soluble, biologically active polyesters. The sequential grafting of an azide-modified camptothecin derivative and PEG allowed for the production of water soluble bioconjugates.¹⁰⁶

Figure 1.9. Propargyl-functionalized monomers synthesized to study click reactions in polyesters



The synthesis of a glycolide monomer with two propargyl groups (Figure 1.9 B) allowed for macromolecules with a higher concentration of pendant alkyne functionality.¹⁰⁷ The polyesters formed in these reactions had high molecular weights ($\langle M_n \rangle$ 5.7×10^4 g/mol;

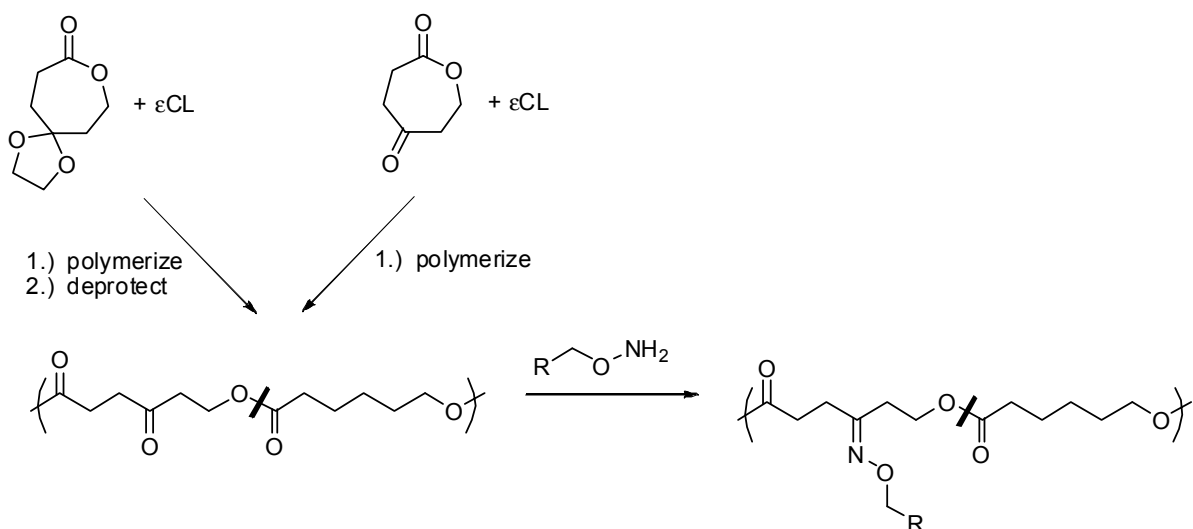
PDI 1.5), and the coupling of PEG and long alkyl chains allowed for the formation of degradable, thermally-responsive polymers exhibiting lower critical solution temperatures.

Functionalized trimethylene carbonate monomers are often employed because they are relatively simple to synthesize, and they copolymerize well with lactides (Section 1.2.3). An alkyne-containing carbonate monomer (Figure 1.9 C) was synthesized and copolymerized with LLA. The resulting poly(ester-carbonate)s had up to 20 mol % of the functional repeat units, and had molecular weights around 1.0×10^4 g/mol.¹⁰⁸ The resulting polymers were grafted with azide-modified saccharides¹⁰⁸ and proteins,¹⁰⁹ allowing these bioconjugates to specifically bind to lectins and antibodies, respectively.

1.3.3 Ketone transformations

The final functional group that has been incorporated into monomers to allow for selective post-polymerization reactions is the ketone. The first ketone-containing polyester was derived from a ketal-containing monomer.⁶⁴⁻⁶⁶ The goal of these syntheses was to obtain alcohol-functionalized polyesters, and this methodology has been addressed in Section 1.2.3 (also see Scheme 1.8). The reports that address the ketone functionality with respect to addition reactions are reviewed here.

First, the high crystallinity of poly(γ -oxo- ϵ -caprolactone) derived from TOSUO was analyzed.¹¹⁰ Later, the synthesis of γ -oxo- ϵ -caprolactone allowed for the direct synthesis of a ketone-containing polyester. The initial studies of copolymers of this monomer with ϵ CL noted similar mechanical and thermal properties of the copolymer to PCL, but ketone-containing repeat units increased the polarity of the devices, which led to faster degradation.¹¹¹



Scheme 1.10. Synthesis of ketone-containing polyesters and subsequent functionalization reactions

Later, the Mayes group synthesized this polyester in a route to functionalized polyesters that was methodologically distinct from previous designs.¹¹² Citing difficulty in the reduction of this ketone-bearing polyester to the alcohol without degradation, they sought more efficient methods to generate functionalized polyesters. By reacting with mild oxyamine nucleophiles, ketone-bearing copolymers could be modified without molecular weight degradation, although these reactions often required long reaction times or large excesses of the oxyamine. A recent report also evaluated the use of sulfonyl hydrazide nucleophiles, although these couplings did not proceed to the high conversions observed with the oxyamine nucleophiles.¹¹³ The coupling of multiple nucleophiles to ketone-containing polyesters was evaluated in sequential and one-pot processes, and each route was found to be an effective way to graft multiple functional groups onto polyesters. Notably, high conversions were reached in shorter reaction times using fewer equivalents of the nucleophile by catalyzing the reaction with a small amount of *p*-toluenesulfonic acid. Ketone-containing

polyesters were also coupled with hydrazines to yield polyesters bearing pendant primary alcohols.¹¹⁴

The study of monomers that contain functional groups whose reactivity is orthogonal to polymerization conditions has advanced the scope of functional aliphatic polyesters significantly. Instead of relying on post-polymerization deprotection steps, these strategies exploit a wide scope of mild, selective functionalization reactions, including substitution, elimination, addition, oxidation, pericyclic reactions, and radical reactions. These monomers often can be formed into homopolymers, or can be copolymerized cleanly with simple aliphatic monomers. In some cases, a series of two or more post-polymerization reactions are required to obtain polyesters that contain the most desirable reactive functional groups (namely carboxylic acids, alcohols, amines or biological functionality).

1.4 Direct functionalization methodologies

In order to avoid numerous post-polymerization reactions, techniques have been sought that will form functionalized macromolecules directly, without the use of protecting groups or other subsequent reactions. If the desired functional group is reactive with alcohols or carboxylic acids, high selectivity is required to form linear polymers exclusively. Other functional groups may be orthogonal to ester-forming reactions, or an ester-containing monomer can be polymerized via mechanisms that are tolerant of various functional groups. Other techniques allow for the direct modification of commercially available aliphatic polyesters in post-polymerization reactions. The methods for the direct formation of functionalized polyesters are reviewed below.

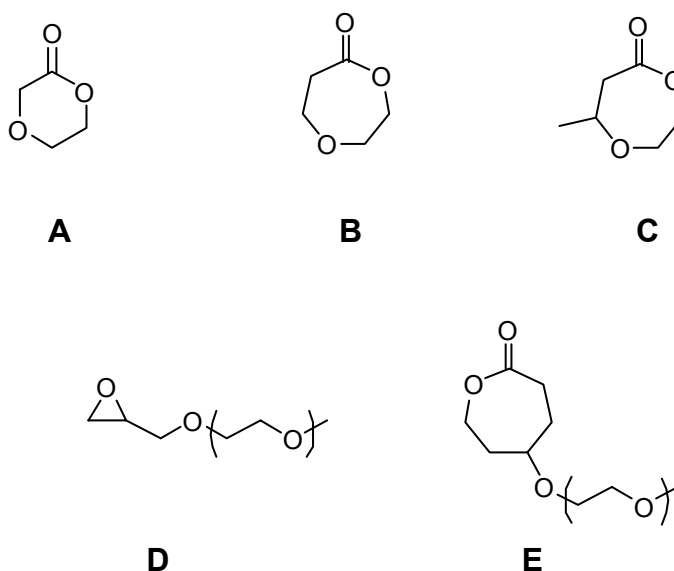
1.4.1 Ester-forming reactions

The first example of an aliphatic polyester that contained a polar functional group was poly(1,4-dioxan-2-one). The monomer (Figure 1.10 A) contains the unreactive ether group, which is well-tolerated in polymerization reactions. The increased polarity of the resulting repeat units imparts unique solubility and thermal properties to these polyesters. The polymer first appeared in the patent literature¹¹⁵⁻¹¹⁷ as a material that could increase the hydrophilicity of degradable sutures relative to other polyesters.¹¹⁸⁻¹²⁰ Further research into different initiator systems,¹²¹ block copolymer synthesis,¹²² and the polymerization mechanism¹²³ further elucidated the properties of this polyester.

The seven-membered lactone, 1,5-dioxepan-2-one (DXO), was also synthesized and polymerized to high molecular weight.^{124, 125} The amorphous homopolymer exhibited a low glass transition temperature (ca. -40 °C) and was indicated as a soft, hydrophilic segment in copolymers. This monomer (Figure 1.10 B) was able to be easily incorporated into a variety of polymers, including random and block copolymers with ϵ CL^{126, 127} or LLA,¹²⁷⁻¹²⁹ crosslinked polyesters,¹³⁰ or copolymers with trimethylene carbonate.¹³¹ Enzyme-catalyzed formation of end-functionalized polyesters¹³² and block copolymers¹³³ was also successful. The seemingly simple inclusion of ether linkages into different macromolecular designs has a drastic effect on the final polymer properties. The degradation of PCL-PDXO copolymers was studied for multiblocks, triblocks, and randomly crosslinked elastomers; the results were compared to PCL.^{134, 135} Keeping the initial ratio of PCL to PDXO at 60 : 40 allowed for the controlled study of the degradation byproducts, rate of mass loss, rate of molecular weight loss, and changes in thermal properties as a function of polymer architecture. Triblock poly(DXO-*b*-CL-*b*-DXO) degraded quickly due to the amorphous, hydrophilic nature of the

outer PDXO blocks. Shorter blocks of PDXO degraded more slowly, as in the case of the random and multiblock copolymers, although their degradation was much faster than PCL. The synthesis of copolymers containing 4-methyl-1,5-dioxepan-2-one (Figure 1.10 C) repeat units also led to polyesters that degraded more quickly than the parent materials.^{136, 137}

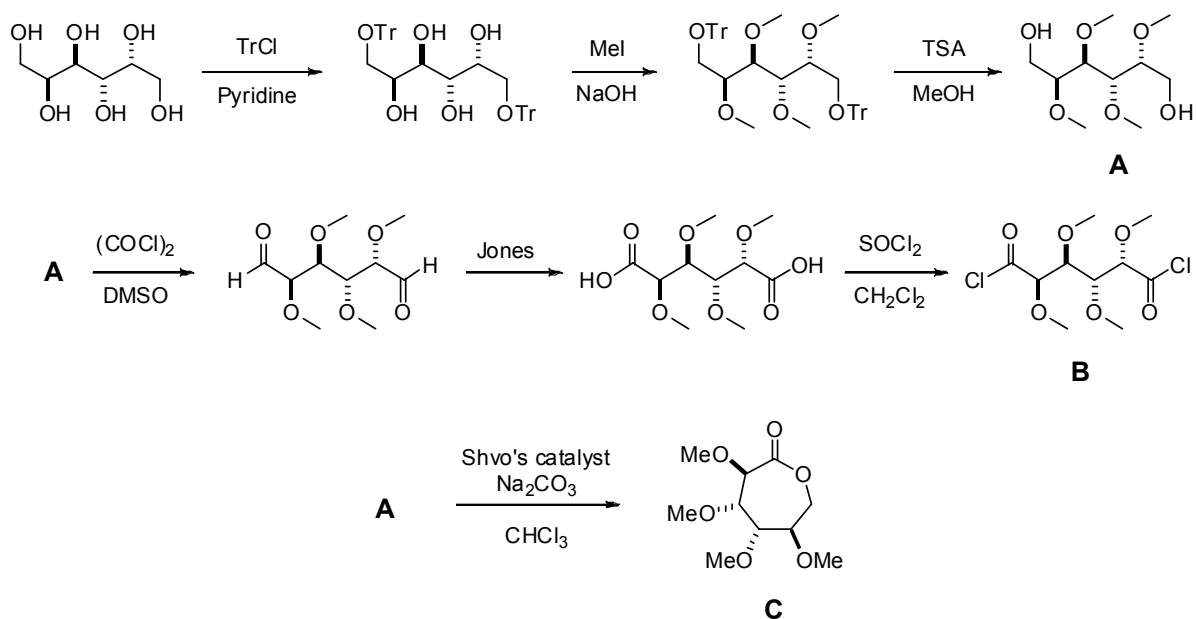
Figure 1.10. Cyclic monomers employed in the synthesis of ether-containing polyesters



As previously mentioned, *trans*- β -hydromuconic acid can be condensed with a variety of diols to form aliphatic polyesters (Scheme 1.9).⁹¹ The inclusion of ether-containing glycols in the step-growth polymerization allowed for amorphous poly(ester-ether)s that exhibited low glass transition temperatures. These liquid polymers could be formed into shape-specific elastomers with very short degradation times and mechanical properties on par with soft tissues.⁹²

The ether group(s) can also be incorporated into the side chain of the polyester instead of the main chain. One way to dramatically increase the amount of ether

functionality in polyesters is to synthesize a polyester grafted with polyethylene glycol. An early example of this strategy made use of an epoxide-terminated PEG (Figure 1.10 D) that was copolymerized with LLA.¹³⁸ Later examples examined the synthesis of a lactone-terminated PEG (Figure 1.10 E) designed to have a similar degree of reactivity with ϵ CL in polyesterification reactions.^{139, 140}

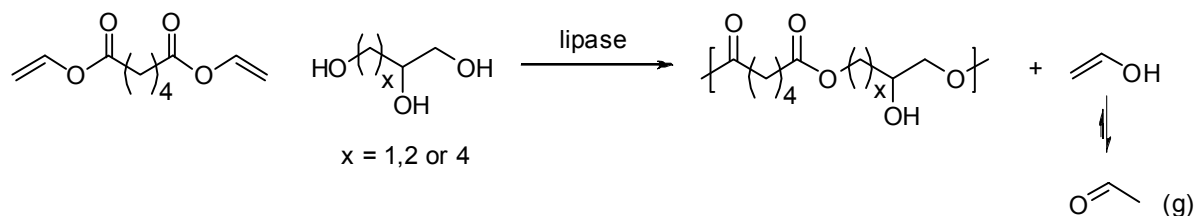


Scheme 1.11. Permethoxylated monomers synthesized for step-growth and chain-growth polymerization

In contrast, a polyester with a high density of methoxy side chains was designed that would provide the high protein resistance of PEG. The monomer syntheses are complex, as shown in Scheme 1.11, but they generate a very high density of ether functionality. Based on the reduced sugar dulcitol, the synthesis of the methoxylated diol, **A**, is the key intermediate. This diol is used as a step-growth monomer, and as a precursor to the diacyl chloride monomer **B** and the lactone monomer **C**. Homopolymers have been synthesized from both

step-growth polymerization of A and B and living ring-opening polymerization of C. The resultant polyesters showed very good resistance to fibrinogen and lysozyme binding, demonstrating that protein absorption can be reduced by increasing the hydrophilicity.^{141, 142}

This body of literature shows that ether functionality can be incorporated easily into polyester backbones and side chains. While this group can impart drastic changes in the polymer solubility and thermal properties, the incorporation of reactive functional groups is a more substantial challenge. In order to accomplish this task, new polymerization reactions were needed that could produce linear aliphatic polyesters from multifunctional monomers. Specialized catalysts and monomer substrates have allowed the implementation of this strategy, although these methods have yet to be robustly developed.



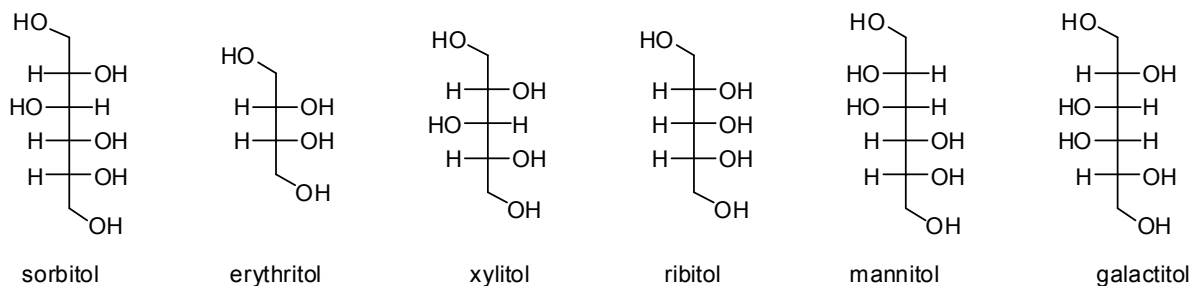
Scheme 1.12. Enzymatic polymerization employed to produce linear, alcohol-functionalized polyesters in a single step

One of the first such examples utilized the regioselectivity of lipase enzymes for primary alcohols to form linear, alcohol-functionalized polyesters in a single step.¹⁴³ By reacting divinyl adipate with either glycerol, 1,2,4-butane triol, or 1,2,6-hexane triol in the presence of Novozym® 435 (commercially available lipase B from *Candida antarctica* immobilized on acrylate resin), no network formation was observed. As shown in Scheme 1.12, linear polyesters with approximately one hydroxyl group per repeat unit were formed

with weight-average molecular weights from 3,000 to 14,000 g/mol. Divinyl esters were chosen to allow for the facile removal of the condensate at the low reaction temperatures used. The selectivity of the enzyme was high, although esterification of some of the secondary alcohols was observed, leading to polydispersity indices between 2.2 and 3.1.

This approach was expanded to include sugar-based polyols. Sorbitol was condensed with divinyl sebacate using lipase catalysis to form linear polyesters with a high degree of alcohol functionality on each repeat unit.¹⁴⁴ The final polymer was isolated in relatively high molecular weight with a controlled distribution, although it was isolated in moderate yields. ($\langle M_n \rangle$ 9.8×10^3 g/mol; PDI 2.1; 64 % yield)

Figure 1.11. Polyol monomers incorporated into functional polyesters by enzymatic polymerizations

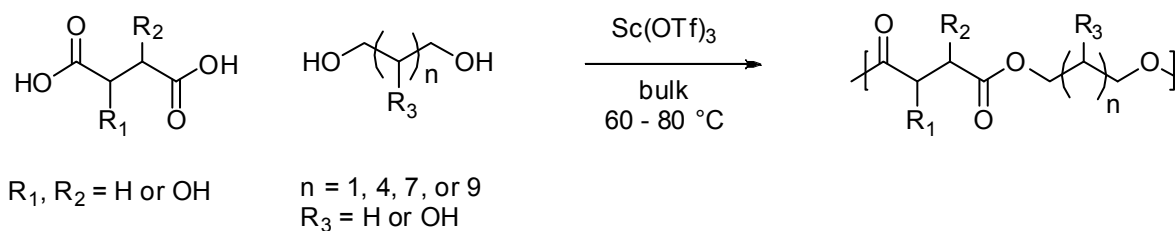


Later reports showed that these enzyme-catalyzed polymerizations could be performed in bulk to yield sorbitol or glycerol-containing polyesters.¹⁴⁵⁻¹⁴⁷ This strategy, which used adipic acid instead of the activated ester, allowed slightly higher molecular weights and lower polydispersities in general. The reaction can also be viewed as a more sustainable alternative due to the lack of reaction solvent and the reduced cost of the diacid monomer, although vacuum must be applied to the system to remove the water condensate.

By varying the ratio of polyol to octanediol in copolymerization reactions, very high molecular weight polyesters with a controlled amount of alcohol functionality could be isolated in high yields. Other sugar-based polyols were also incorporated into the polyesters, and it was found that the stereochemistry of the secondary alcohols had a pronounced effect on the final molecular weight of the polyesters.¹⁴⁸ Unfortunately, no clear correlations between the polyol monomers used (Figure 1.11) and final molecular weights could be deduced.

A similar enzymatic polymerization was used to produce polyesters bearing carboxylic acid groups.¹⁴⁹ In this case, bis(hydroxymethyl)butyric acid allowed for the formation of copolymers with a limited amount of carboxylic acid functionality. The reactivity of this diol was poor, and therefore homopolymerizations were not reported. An copolymer derived from adipic acid and an equimolar mixture of bis(hydroxymethyl)butyric acid and 1,8-octanediol had a number-average molecular weight of only 1.2×10^3 g/mol.

A second ester-forming methodology that allows for linear alcohol-containing polyesters in a single step is the use of Group 3 or lanthanide metal catalysts.¹⁵⁰ Initial reports of the reactivity of these metal catalysts, including $\text{Ln}(\text{OTf})_3$, $\text{Sc}(\text{OTf})_3$, and $\text{Sc}(\text{NTf})_3$, indicated that diacids and diols could be condensed to high molecular weight polyesters at mild temperatures under vacuum.^{151, 152} It was further shown that these systems exhibited selectivity for primary alcohols for a large scope of monomers, including tartaric acid, malic acid, glycerol and sorbitol (Scheme 1.13). For example, malic acid was condensed with 1,9-nonanediol using $\text{Sc}(\text{OTf})_3$ at 80 °C for 7 hours to yield a polymer with number-average molecular weight of 1.3×10^4 g/mol (PDI 2.2).



Scheme 1.13. Synthesis of linear polyesters having hydroxyl groups via selective Lewis acid catalysis

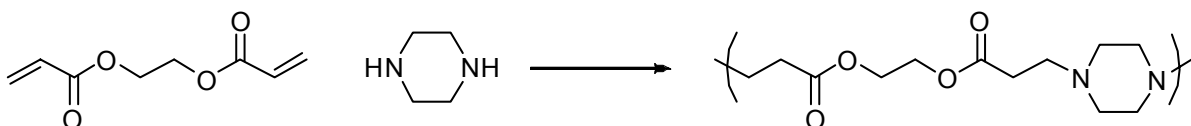
While these techniques allow the formation of functional linear polyesters in a single step in high molecular weight, the scope of these methodologies is quite narrow. The results of any given reaction are highly substrate dependant and require expensive catalysts and stringent reaction conditions.

1.4.2 Ester-containing monomers

In order to form degradable functional polyesters directly in a single step, the synthesis and polymerization of ester-containing monomers has been investigated. Conjugate additions, radical ring-opening polymerizations, and metathesis reactions are all tolerant of a variety of functional groups, including esters, and each has been used to this end.

One of the earliest reports of this type of synthesis came from researchers primarily interested in the formation of poly(amino amide)s by the conjugate addition of diacrylamides and piperazine derivatives. The replacement of the diacrylamide with a diacrylate resulted in the first synthetic amine-functionalized polyesters.¹⁵³ By reacting piperazine or 2-methyl-piperazine with a small set of alkyl and aromatic diacrylates, a small series of these polyesters was synthesized and characterized (Scheme 1.14). The group further pursued

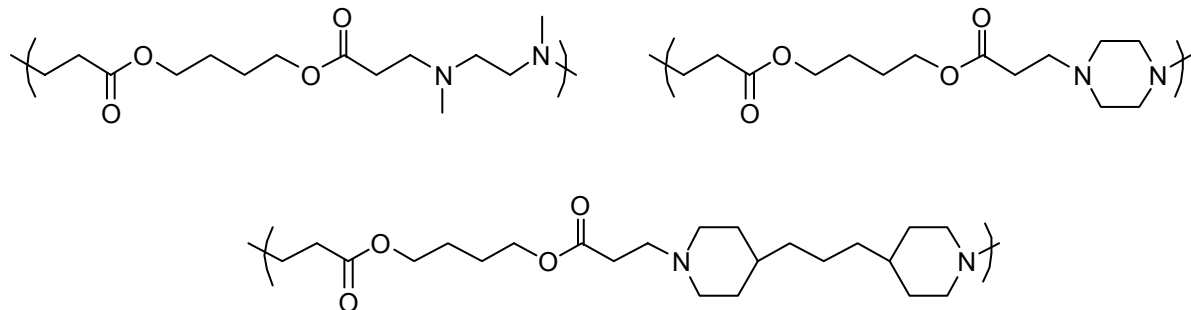
polyamide research, and the polyester work lay dormant for many years, despite the fact that this attractive step-growth polymerization takes place under mild heating without catalyst and without generating any reaction byproducts.



Scheme 1.14. Conjugate addition reaction used to synthesize amine-containing aliphatic polyester in a single step

Thirty years later, the Langer group revived this conjugate addition strategy to study amine containing polyesters as gene transfection vectors.¹⁵⁴ This strategy proved to be an efficient way to synthesize poly(β -amino ester)s with a wide variety of structures and functionality from commercially available starting materials using simple, mild reaction conditions. The first report from this group studied the polymerization of 1,4-butanediol diacrylate with *N,N'*-dimethylethylenediamine, piperazine, or 4,4'-trimethylene dipiperidine in solution reactions to yield polyesters of moderate to high molecular weights ($\langle M_n \rangle$ 6 – 32 x 10³ g/mol; PDI 1.5 – 2.5). The tertiary amines were found to be unreactive in further conjugate addition reactions, ensuring the polymers would be linear, as shown in Figure 1.12. Also, the selectivity of the amines for acrylate addition instead of carbonyl addition ensured that amine-containing polyesters were formed instead of amides. The polymerizations were conducted in solvent (tetrahydrofuran or methylene chloride) at 50 °C for 48 h.

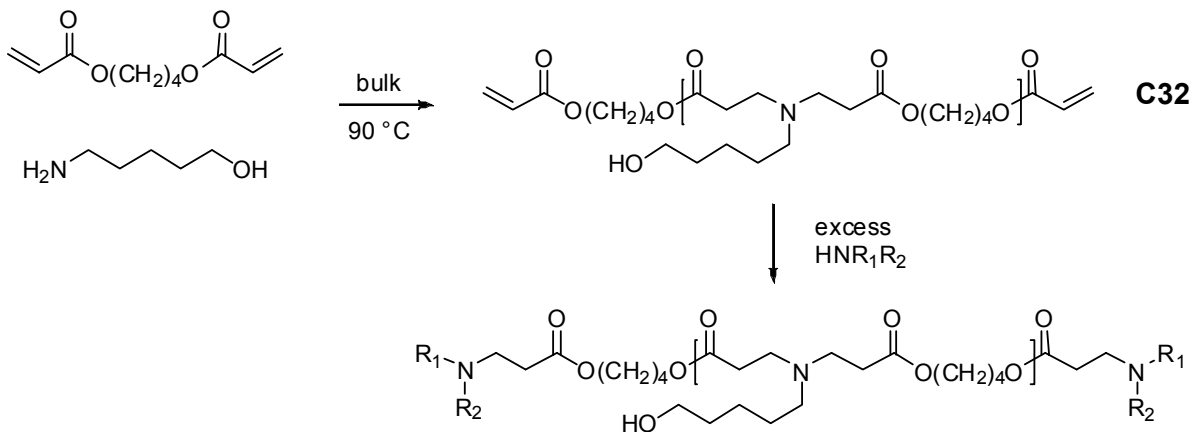
Figure 1.12. Amine-containing polyesters by conjugate addition



One of the primary disadvantages of this reaction was the small number of commercially available secondary diamines that could be incorporated, which inherently limited the diversity of structures that could be studied. The conjugate addition polymerization strategy was expanded to include primary amines, which greatly increased the types of functional groups that could be included in aliphatic polyesters.^{155, 156} A library of 140 polymers was synthesized in parallel by reacting each diacrylate and amine combination in methylene chloride at 45 °C for 5 days. Later, this synthesis was expanded to a library of 94 amines and 25 diacrylates (2350 unique polymers), including those containing with ether, alcohol, siloxane, thio-ether, amide, heterocyclic, and fluorinated alkane groups.¹⁵⁷

Materials that performed well in gene transfection experiments often had at least one of these common traits: a hydrophobic diacrylate monomers, an alcohol or imidazole side groups, and/or a linear secondary diamine. As previously mentioned, these studies were conducted in large parallel arrays. One disadvantage of this high-throughput system is the assumption that each polymerization mixture resulted in the optimal material made up of that repeat unit. In order to study molecular weight and end-group effects, the stoichiometry of these polymerization reactions was varied.¹⁵⁸ By performing these step-growth

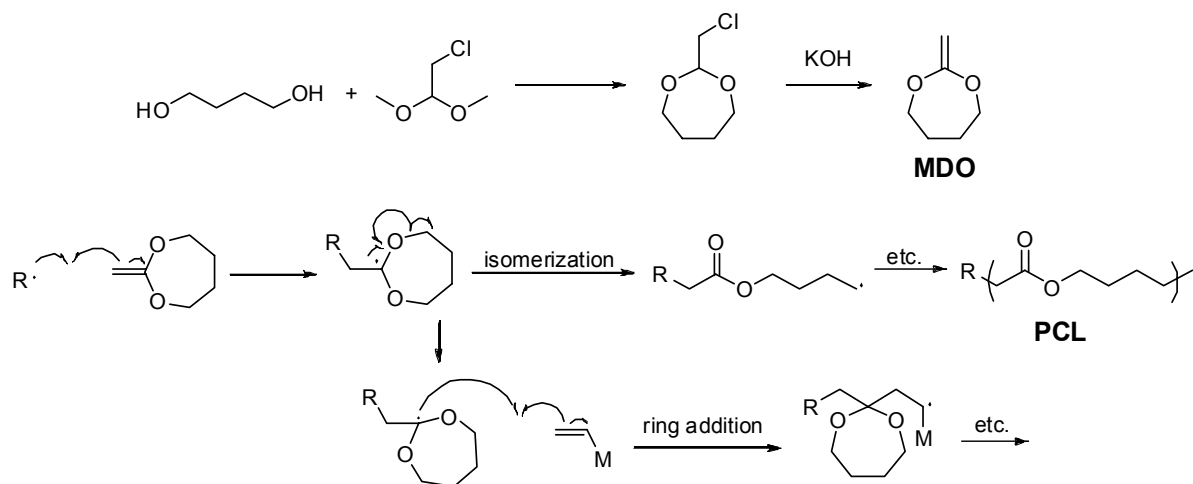
polymerizations in bulk at 100 °C for 5 h, polymers were isolated with weight-average molecular weights between $4 - 18 \times 10^3$ g/mol and either acrylate or amine end groups. It was found that materials with acrylate end groups were ineffective in transfection experiments, and that the materials with the highest molecular weight performed the best. One of these polymers, C32, was further studied as a transfection agent *in vivo* (Scheme 1.15).¹⁵⁹ The end groups of C32 were varied by first synthesizing an acrylate-terminated polymer, and then reacting it with excess amines.^{160, 161} Again, it was found that the structure of the end groups had a pronounced effect; those with hydrophobic spacers terminated in primary amines or alcohols worked best.



Scheme 1.15. Synthesis of poly(β-amino ester) C32 with a variety of end groups

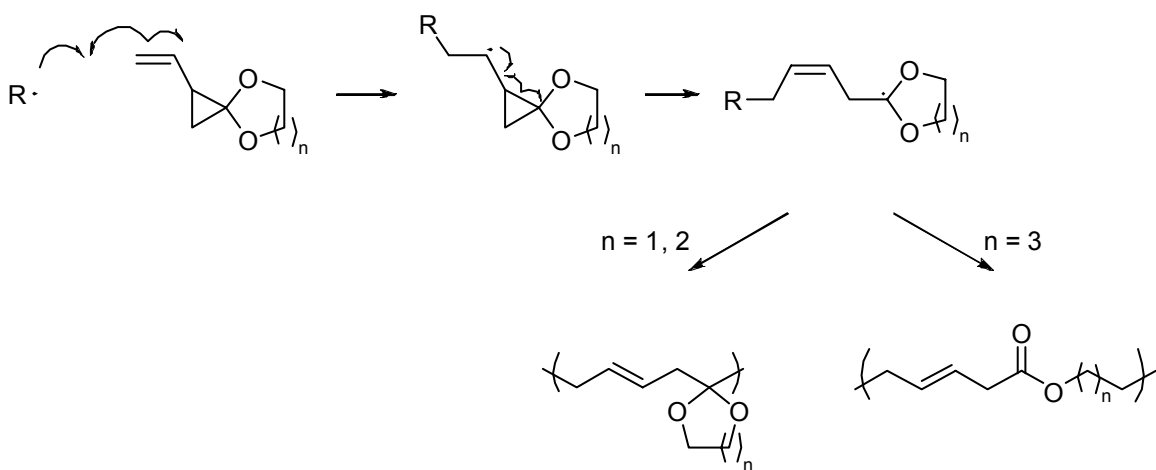
Another functional-group tolerant polymerization that has been used to form polyesters is the free radical ring-opening polymerization of 2-methylene-1,2-dioxepane (MDO) to form poly(ε-caprolactone).¹⁶² The synthesis of this monomer and its radical polymerization mechanism is shown in Scheme 1.16. The polymerization of corresponding 5- and 6-membered analogues of this monomer resulted in unwanted ring additions, a

competing side reaction to ring-opening. In order to reduce the amount of ring addition, monomers that stabilize the propagating radical at a secondary or benzylic carbon were synthesized and copolymerized with styrene, 4-vinyl anisole, methyl methacrylate, vinyl acetate, and 4-vinyl pyridine.¹⁶³⁻¹⁶⁵ Later reports have shown that MDO can form copolymers with vinyl phosphonic acid,¹⁶⁶ dimethyl vinylphosphonate,¹⁶⁶ *N*-vinylpyrrolidinone,¹⁶⁷ methyl acrylate,¹⁶⁸ *N*-isopropylacrylamide,¹⁶⁹ diacrylamides,¹⁶⁹ and vinyl monomers with fluorinated side chains.¹⁷⁰ The main drawback of this strategy is that MDO is generally much less reactive in free-radical polymerizations than other monomers, resulting in difficulty controlling the repeat unit composition and distribution. Despite this disadvantage, this method has allowed the single-step synthesis of degradable polymers that contain a wide range of functional groups.



Scheme 1.16. Synthesis and mechanism of MDO free radical ring-opening polymerization of poly(ϵ -caprolactone)

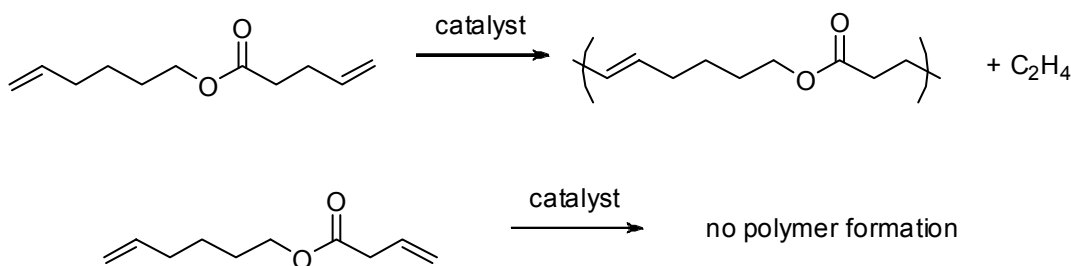
Another acetal monomer that can participate in radical ring-opening polymerization contains a vinylcyclopropane group.¹⁷¹⁻¹⁷⁴ The resulting polymer structure is likewise dependant on the size of the ring; monomers containing five- or six-membered acetals result in ring addition polymers, while seven-membered rings result primarily in unsaturated polyesters from ring opening (Scheme 1.17). Again, the use of alkyl or aryl side chains to create a more stable propagating radical enhanced the degree of ring-opening.¹⁷⁵



Scheme 1.17. Radical ROP of vinylcyclopropane cyclic acetal monomers

Metathesis polymerization is the final example of a functional group tolerant polymerization method that has resulted in functionalized aliphatic polyesters. Acyclic diene metathesis (ADMET) polymerization was first used to synthesize unsaturated polyesters by Wagener, *et al.*^{176, 177} In these early examples, molybdenum or tungsten catalysts were employed to study the polymerization of the ester-containing dienes shown in Scheme 1.18. While the polymerization of dienes with a sufficient number of methylene spacers between the double bond and the ester group was successful in a short time ($\langle M_n \rangle$ 1.8×10^4 g/mol; PDI 1.9; 8h), monomers with shorter spacers were unsuccessful. This was explained by the

negative neighboring group effect, which hypothesized that either the olefin is polarized by the ester group, or that the carbonyl comes in close proximity to the metal, which allows Lewis acid coordination and deactivation of the catalyst.



Scheme 1.18. ADMET of ester-containing dienes to form unsaturated polyesters

Later mechanistic studies hypothesized that high molecular weight polymers formed by ADMET of ester-containing dienes could undergo cyclodepolymerization to form oligomers and macrocyclic oligomers.^{178, 179} By conducting these reactions at high concentrations, linear polymers were favored over cyclic oligomers by an entropy-driven ring-opening polymerization.

In order to form polymers with a variety of structural groups, chiral unsaturated poly(ester-co-amide)s with isopropyl or isobutyl side groups were synthesized by ADMET.¹⁸⁰ Again, the negative neighboring group effect was observed, but monomers with a sufficient number of methylene spacers between the ester or amide groups and the olefin were successfully polymerized to high molecular weights.

Segmented copolymers containing aliphatic polyester hard segments were also synthesized by ADMET. By utilizing olefin end-functionalized poly(tetramethylene oxide) (PTMO) as the soft segment, polyester formed by ADMET could be chain-extended to a high

molecular weight segmented multiblock copolymer.¹⁸¹ The final number-average molecular weight of the copolymer was 2.4×10^4 g/mol; PDI 1.4. However, the aliphatic polyester hard segment had inferior thermal properties to polycarbonate or aromatic polyester based materials.

Metathesis reactions were crucial in the preparation of mechanically interlocked polymers.¹⁸² Initial steps formed a mechanically interlocked dimer by ring-closing methathesis. Terminal alcohol groups on these “daisy-chain” type molecules were transformed to esters with 4-pentenoic acid, resulting in terminal dienes. The high functional group tolerance of the ADMET process allowed these interlocked monomers to be condensed into polyesters with a very unique structure.

One final example of the use of metathesis polymerization relies on ring-opening of a previously discussed unsaturated ϵ -caprolactone, shown in Figure 1.6 B.⁹⁰ This monomer was polymerized by ROMP to a number-average molecular weight of 6.0×10^4 g/mol; PDI 2.1. The monomer could also participate in copolymerizations with norbornene, 1-cyclooctaene, and 1,5-cyclooctadiene.

The polymerization of ester-containing monomers to form functionalized polyester directly has been met with varying degrees of success, depending on the technique employed. Highly selective step-growth methodologies result in linear polymers, but with a fairly narrow substrate scope. Conjugate additions result in amine-containing material; radical ring-opening polymerizations can result in high molecular weight polymers; and ADMET polymerizations result in unsaturated polyesters. Each of these techniques is tolerant of a wide range of functional groups.

1.4.3 Direct modifications

Given the sometimes narrow scope of functional monomer techniques, researchers have turned to more robust methods for easily functionalizing polyesters, especially modifying the surface properties of polyesters. Several procedures have been developed that rely on the irradiation of a polymer to induce surface reactions or crosslinking. Often the irradiation is conducted in the presence of a small molecule or vinyl monomer, which results in a functionalized surface or graft copolymer. Several combinations of irradiation techniques and small molecule grafting partners have been demonstrated, and a few noteworthy examples are discussed.

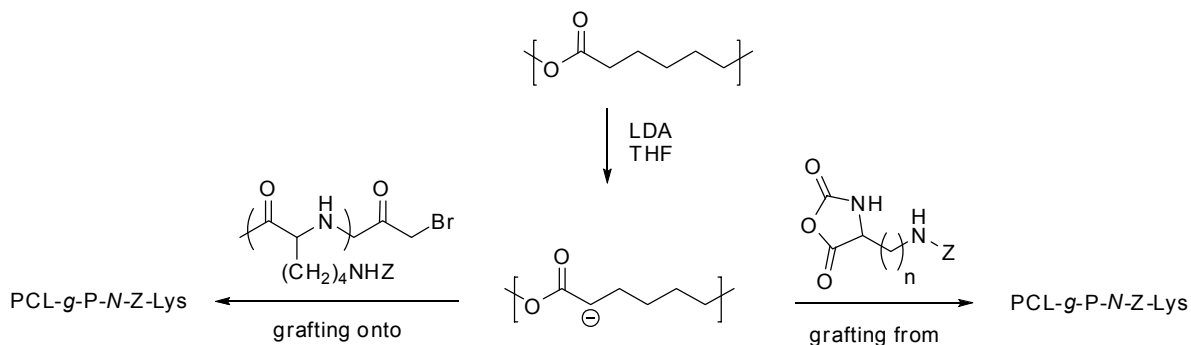
Gamma rays have been used to grow polystyrene from poly(3-hydroxybutyrate) and poly(3-hydroxyvalerate) surfaces.¹⁸³ Polylactide^{184, 185} and PLGA¹⁸⁶ have been exposed to microwave ammonia plasma to generate amide and amine-functionalized surfaces. PLLA was exposed to hydrogen peroxide solutions under UV light to generate radical macroinitiation sites, after which the surface was exposed to hydroxyethyl methacrylate, methacrylic acid, or acrylamide to form functional surfaces.¹⁸⁷ Gas plasma has also been used to modify the surface roughness of PDLLA.¹⁸⁸ Crosslinking has been accomplished by exposure of PLA to gamma rays¹⁸⁹ or e-beam.¹⁹⁰ Electron beam techniques have also been used to form a poly(acrylic acid)-grafted PCL copolymer which was later studied in cell culturing experiments.¹⁹¹

While these techniques can cause drastic changes to the surface properties, thermal stability, and mechanical properties of a polyester, they are not generally applicable. Controlling these reactions is difficult, and exposure of polyesters to these harsh conditions can cause unwanted polymer degradation or crosslinking. A more controlled approach to

surface modification was described in which PLLA can be grafted with acrylamide, maleic anhydride, or *N*-vinyl pyrrolidinone in a single step. Briefly, the polymer was exposed to the vapor of the desired monomer and benzophenone, and the entire system was exposed to UV light.^{192, 193} GPC analysis was conducted both on polymers exposed to these conditions and to e-beam methods,¹⁹¹ and it was found that the monomer vapor technique degraded the polymer to a lesser extent. Later studies showed that PLLA or PCL could be successfully modified this way to create surfaces favorable for incubation of mesenchymal stem cells.¹⁹⁴

The previous techniques were effective at modifying the surfaces of aliphatic polyesters, but one method has been reported for modifying PCL in solution in a single step. By forming a poly(enolate) using LDA, functional polyesters were isolated after reaction with a variety of electrophiles.¹⁹⁵ Formation of the polymeric enolate led to intra- and intermolecular backbiting and degradation, but quenching with aldehydes, ketones, acyl chlorides, or alkyl halides allowed the corresponding alcohol or carbonyl grafted polyesters. The yields of these reactions were good, but the conditions required to reach high conversions led to degradation. A later report showed that carboxylic acid functionalized PCL could be isolated by reacting the poly(enolate) with carbon dioxide. In this example, the precursor had a number average molecular weight of 5.4×10^4 g/mol and PDI of 1.5; after a reaction with 0.5 or 1.0 equivalents of LDA and excess CO₂, the polymer had degraded significantly. ($\langle M_n \rangle = 1.8 - 2.0 \times 10^4$ g/mol; PDI 3.9-4.1; 7 – 11% conversion) The poly(enolate) strategy was also employed in the synthesis of amine-containing PCL graft copolymers.¹⁹⁶ The synthesis of the appropriate coupling partners allowed for the copolymers to be formed by either “grafting onto” or “grafting from” techniques, as shown in Scheme 1.19. In order to graft onto PCL, the poly(*N*-Z-lysine) needed be formed in

advance with a halogen end group. Upon formation of the carbanionic PCL, the polyamide chains were grafted onto the main chain by substitution reactions. Alternatively, the poly(enolate) could be formed, and each nucleophilic site acted as an initiator for the activated lysine monomer to form a poly(*N*-Z-lysine) chain.



Scheme 1.19. Synthesis of graft polymers by poly(enolate) formation

These direct modification procedures are attractive because they use commercially-available polymers and are able to vastly change the properties of these degradable materials. These technologies are not yet broadly applicable, but are especially attractive for surface modifications.

1.5 Conclusions

The utility of aliphatic polyesters like PLA, PGA, and PCL comes from their biological compatibility and degradability. Since these materials are inherently limited in their thermal, mechanical, and solubility properties, prolific research has been conducted to modify these properties by forming the corresponding functional polymers. The drive to increase the hydrophilicity of the polymers and to include sites for grafting useful small

molecules has yielded materials with reactive carboxylic acids, amines, and alcohols. These have been largely derived from monomers containing protected functional groups. Other functional groups that have been exploited include halogens, azides, olefins, alkynes, and ketones; these groups have the distinct advantage of not requiring a deprotection step after the polymerization reaction, although their transformation to a more desired functionality can require multiple steps. Other advanced techniques have sought to incorporate the desired functional groups into the polyester in a single step. Examples of ester-forming polymerizations or ester-containing monomers polymerized by other bond-forming techniques have allowed for the controlled synthesis of functional polymers in one step. Several techniques for the direct modification of aliphatic polyesters have been demonstrated, although control of these reactions can often be a limiting factor.

1.6 Dissertation Organization

This dissertation describes step-growth polymerization methods to synthesize a broad range of functional aliphatic polyesters. The first chapter is a survey of the literature on functional polyesters and is divided into three sections based on the type of technique used to develop the materials. Chapters two through four discuss specific methodologies for the synthesis of functional linear polymers and degradable elastomers. Chapter two discusses the use of Diels-Alder chemistry to synthesize aliphatic polyesters and polyester-based elastomers. The scope of this method is explored with respect to amine and ether functionality. Chapter three describes the synthesis of azide-containing polyesters and their application in gene delivery devices. Chapter four briefly discusses the structure-property relationships behind the degradation of the Diels-Alder elastomers. Chapter five concludes

the dissertation with a discussion of the research and its possible future directions. Supplemental data, including spectra, chromatograms, and thermal characterization, are included in the appendices. Chapter two has been published in *Macromolecules*,¹⁹⁷ and chapters three and four will be submitted for publication in peer-reviewed journals.

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Chapter 2

AMORPHOUS UNSATURATED ALIPHATIC POLYESTERS DERIVED FROM DICARBOXYLIC MONOMERS SYNTHESIZED BY DIELS-ALDER CHEMISTRY

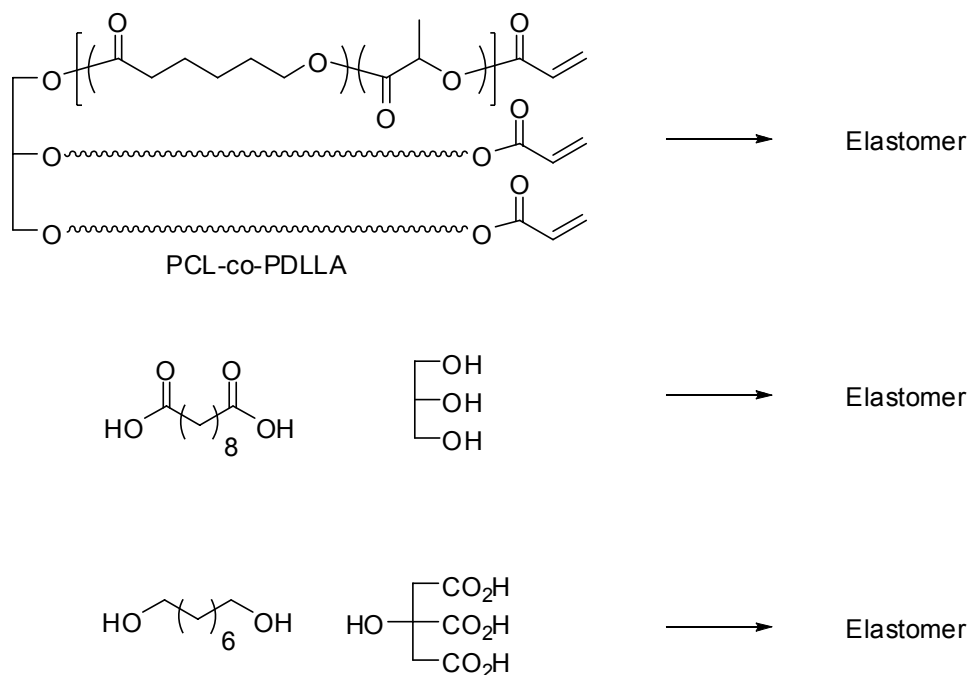
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2.1 Introduction

The use of aliphatic polyesters in biological and medical applications is well established because of their intrinsic biodegradability and biocompatibility. The most common materials are synthesized by ring opening polymerization (ROP), including poly(L-lactic acid) (PLLA), poly(glycolic acid) (PGA), poly(ϵ -caprolactone) (PCL), and their copolymers. Uses for these polyesters include drug delivery,¹ tissue engineering scaffolds,² stents,³ and sutures.⁴ The majority of these polyesters are semicrystalline, hydrophobic polymers that lack reactive functional groups along the backbone. This set of properties may limit their utility in certain applications. For example, the ideal drug delivery devices have a linear degradation and release profile over time. However, the semicrystalline, hydrophobic materials mentioned above have a nonlinear biodegradation profile due to poor water permeability and poor solubility in aqueous systems. Also, in tissue scaffolds, it may be necessary to have a soft, flexible matrix which mirrors the mechanical properties of the surrounding tissues. In these instances, the aliphatic polyesters mentioned fall short due to their relatively brittle, rigid nature in physiological environments.

Recent efforts have sought synthetic means to form amorphous aliphatic polyesters that will be able to meet these property requirements by changing the topology of the materials and by incorporating polar functional groups along the backbone of the polyesters. For example, Amsden has taken advantage of the amorphous nature of poly(D,L-lactic acid) (PDLLA) and its copolymers by incorporating it into acrylate end-capped star copolymers.⁵ These materials were completely amorphous and formed amorphous elastomers upon photocuring of the thermoplastic precursor. The crosslinking density was adjusted by varying the length of the arms of the stars. Langer described a tough biodegradable

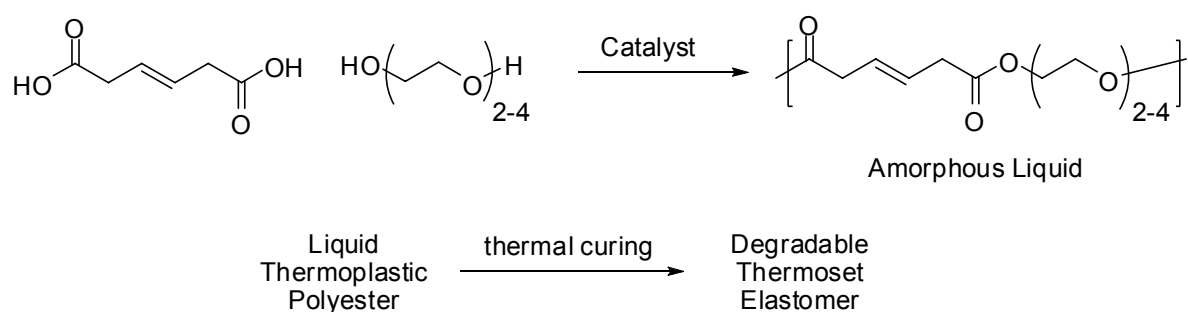
elastomer synthesized from the step growth condensation of glycerol and sebacic acid that, despite being semicrystalline, was above all thermal transitions and totally amorphous at the intended use temperature of 37 °C.⁶ A similar elastomer was reported by Ameer, who used citric acid and 1,8-octanediol as the monomers.⁷ The latter two examples rely on step growth condensations of monomers with an average monomer functionality greater than two ($f_{av} > 2$) to ensure that the thermoset materials were lightly crosslinked after the reaction proceeded to high conversion. This required the materials to be cured at high temperature under vacuum on the order of days. In addition, the final crosslinking density of the materials was difficult to control.



Scheme 2.1. Examples of amorphous aliphatic polyesters from Amsden, Langer, and Ameer

A significant advancement was realized by our group in this field with the design of new amorphous degradable elastomeric thermoset materials that combine the amorphous

nature of thermoset materials with the synthetic and processing ease of thermoplastic elastomers.⁸ The step growth polymerization of trans- β -hydromuconic acid and oligo(ethylene glycol)s yields unsaturated polyester materials (Scheme 2) that can be thermally crosslinked in the presence of a radical initiator. This approach relies on the use of an amorphous linear prepolymer that has a low glass transition temperature and is a liquid at room temperature. The crosslinking density of the material is easily modified to alter the mechanical properties ($G = 0.02 - 20$ MPa). The prepolymer composition is readily changed to tune the degradation rate of the material (linear mass loss up to 100 % in as little as 30 days).



Scheme 2.2. Rapidly degrading elastomeric materials synthesized by Olson, *et al.*⁸

While these materials overcome many of the obstacles previously described, their thermal properties are intrinsically linked to their solubility via the nature of the ether-containing diol used in the polyester synthesis. Including the oligo(ethylene glycol) ensures that the material cannot crystallize and has a low glass transition temperature, while at the same time causing the material to be hydrophilic. It may be necessary to form materials whose thermal and solubility properties are independent of each other, or to otherwise further modify the final properties of the elastomer. To do so, it is desired to modify the liquid

polyester to contain various polar functional groups. Most previous examples of functionalized aliphatic polyesters are based on the ROP of a lactone or lactide containing the functionality.⁹ Illustrative materials include those synthesized to contain amino,¹⁰⁻¹¹ carboxyl,¹² and hydroxyl¹³⁻¹⁵ groups. These functional monomers are often copolymerized with lactide or a lactone, and thus have thermal properties that represent the average of the base material and the functionalized material. This approach makes it difficult to simultaneously target a specific degree of functionality and specific thermal transition temperatures.

In order to form a functionalized polyester that can serve as an amorphous, liquid precursor to degradable elastomers, a methodology needed to be developed that would meet several requirements. The first criteria are that the system allows for incorporation of a range of functional groups to be incorporated into the materials, while at the same time ensuring the polyesters are completely amorphous liquids at room temperature. Also, the materials must have a site of reaction for crosslinking. Lastly, each polyester must be able to be synthesized to a targeted molecular weight. Herein, we describe a synthetic methodology that relies on Diels-Alder chemistry to meet these criteria and to achieve unsaturated, amorphous, functionalized polyesters.

2.2 Experimental Section

Materials. All reagents were purchased from Aldrich and used without further purification unless otherwise noted. Pure 5-norbornene *cis*-2,3-dicarboxylic acid (Diacid I) was recrystallized from ethanol and water. Pure 1,8-octanediol was recrystallized from tetrahydrofuran.

Diels-Alder reactions of diethyl fumarate. *4-Methylcyclohex-4-ene trans-1,2-dicarboxylic acid (Diacid II).* Isoprene (34 g, 500 mmol) and diethyl fumarate (86 g, 500 mmol) were refluxed in toluene for 24h. The reaction mixture was reduced by rotary evaporation and then purified by column chromatography over silica gel. The typical eluent was 25 % acetone in hexanes. Water and THF in equal parts were used to dissolve 3 equivalents of lithium hydroxide and the pure diester. The mixture was refluxed for 24h, extracted with ether, washed with brine, dried with magnesium sulfate, and concentrated to yield the crude diacid in quantitative yield. The diacid was recrystallized from ethanol and water to give the pure diacid in 55 % yield. ^1H NMR (400 MHz, *acetone-d₆*) δ (ppm) 5.44-5.37 (m, 1H), 2.76 (dtd, $J = 37.3, 10.6, 10.6, 5.7$ Hz, 2H), 2.47-2.06 (m, 4H), 1.67 (s, 3H). ^{13}C NMR (100.61 MHz, *acetone-d₆*) δ (ppm) 177.32 (-CO₂H), 177.18 (-CO₂H), 134.09 (=C(CH₃)CH₂-), 120.88 (=C-H), 43.20 (-CH-CO₂H), 42.58 (-CH-CO₂H), 34.10 (-CH₂-C(H)=), 29.78 (-CH₂-C(CH₃)=), 24.18 (-CH₃). High resolution mass spectrum calcd for C₉H₁₂O₄+H: 185.081. Found: 185.080. Calcd for C₉H₁₂O₄+Na: 207.063. Found: 207.062. Melting point = 170 °C.

4,5-Dimethylcyclohex-4-ene trans-1,2-dicarboxylic acid (Diacid III). Fumaric acid (58 g, 500 mmol) and 2,3-dimethyl-1,3-butadiene (41 g, 500 mmol) were refluxed in ethanol for 4 days. The reaction mixture was concentrated by rotary evaporation. Water was then added and the mixture was extracted with ether. The combined ether extracts were washed with brine, dried with magnesium sulfate, and concentrated to give the product as a white solid in quantitative conversion. The crude product was recrystallized from ethanol and water to give the pure product in 56 % yield. ^1H NMR (400 MHz, *acetone-d₆*) δ (ppm) 10.70 (s, 2H), 2.75 (m, 2H), 2.36-2.07 (m, 4H), 1.64 (s, 6H). ^{13}C NMR (100.61 MHz,

acetone-d₆) δ (ppm) 177.56 (-CO₂H), 125.62 (=C(CH₃)CH₂-), 43.45 (-CH-CO₂H), 35.75 (-CH₂-C(CH₃)=), 19.72 (-CH₃). High resolution mass spectrum calcd for C₁₀H₁₄O₄+H: 199.097. Found: 199.098. Calcd for C₁₀H₁₄O₄+Na: 221.079. Found: 221.079. Melting point = 233 °C.

4-(N,N-Diethylaminomethyl)cyclohex-4-ene trans-1,2-dicarboxylic acid (Diacid IV). 2-(*N,N*-Diethylaminomethyl)-1,3-butadiene was synthesized as previously reported.²¹ This diene (22.4 g, 160 mmol) was then added to a flask containing a solution of fumaric acid in ethanol (18.6 g, 160 mmol in 300 mL ethanol). The mixture was brought to reflux and stirred for 5 days. The solid product precipitated out of ethanol and was filtered and rinsed with ethanol to yield the pure product in 80 % yield. ¹H NMR (300 MHz, D₂O) δ ppm 6.04 (s, 1H), 3.69 (s, 2H), 3.18 (tt, *J* = 13.3, 13.3, 6.5, 6.5 Hz, 4H), 2.84-2.69 (m, 2H), 2.60-2.03 (m, 4H), 1.27 (t, *J* = 7.3, 7.3 Hz, 6H). ¹³C NMR (100.61 MHz, D₂O) δ (ppm) 186.49 (-CO₂H), 186.39 (-CO₂H), 137.87 (=C-CH₂N-), 131.42 (=C-H), 63.48 (-CH₂-N-), 52.09 (-N-CH₂-), 48.84 (-CH-CO₂H), 47.94 (-CH-CO₂H), 34.86 (-CH₂-CH=), 33.44 (-CH₂-C(CH₂N(CH₂CH₃)₂)=), 13.43 (CH₃). High resolution mass spectrum calcd for C₁₃H₂₁O₄N+H: 256.155. Found: 256.151. Calcd for C₁₃H₂₁O₄N+Na: 278.137. Found: 278.134. Melting point = 193 °C.

Diels-Alder reactions of maleic anhydride. A representative example for 5-norbornene *cis*-2,3-dicarboxylic anhydride (Anhydride I) follows. Dicyclopentadiene was cracked according to literature procedures and then the cyclopentadiene (30 g, 450 mmol) immediately used in a subsequent Diels-Alder reaction with maleic anhydride (45 g, 450 mmol) in refluxing toluene. The reaction mixture was allowed to reflux for one hour and then the solvent was removed by evaporation at reduced pressure. The crude product was

isolated in 100 % yield and then recrystallized from methanol. The pure product was isolated in 51 % yield. ^1H NMR (400 MHz, CDCl_3): δ (ppm) 6.28 (d, 2H, $J = 2.0$ Hz), 3.57 (m, 2H), 3.48 (d, 2H, $J = 1.6$ Hz), 6.28 (d, 2H, $J = 2.0$ Hz), 1.65 (dd, 2H). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 171.33 (-CO₂-), 135.41 (=CH-), 52.64 (-CHC=), 46.97 (bridgehead), 45.98 (CHCO₂-). High resolution mass spectrum calcd for C₉H₈O₄+H: 165.055. Found: 165.058. Calcd for C₉H₈O₃+Na: 187.037. Found: 187.039. Melting point = 97 °C.

4-methylcyclohex-4-ene cis-1,2-dicarboxylic anhydride (Anhydride II). Isoprene was used as the diene. 52 % yield. ^1H NMR (300 MHz, CDCl_3) δ ppm 5.62 (ddd, $J = 8.2, 3.5, 1.8$ Hz, 1H), 3.48-3.27 (m, 2H), 2.74-2.11 (m, 4H), 1.76 (s, 3H). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 174.47 (-CO₂-), 174.31 (-CO₂-), 136.49 (=C(CH₃-), 120.04 (=CH-), 39.98 (-CHCO₂-), 39.35 (-CHCO₂-), 28.29 (-CH₂-CH=), 23.96 (-CH₂-C(CH₃-), 23.37 (-CH₃). High resolution mass spectrum calcd for C₉H₁₀O₃+Na: 189.053. Found: 189.055. Melting point = 68 °C.

4,5-Dimethylcyclohex-4-ene cis-1,2-dicarboxylic anhydride (Anhydride III). 2,3-Dimethyl-1,3-butadiene was used as the diene. 65 % yield. ^1H NMR (400 MHz, CDCl_3) ppm 3.48 (dt, $J = 4.7, 4.4, 2.2$ Hz, 2H), 2.52 (td, $J = 3.5, 1.7, 1.7$ Hz, 4H), 2.27 (s, 6H). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 174.49 (-CO₂-), 127.23 (=C(CH₃-), 40.30 (-CHCO₂-), 30.37 (-CH₂-), 19.19 (-CH₃). High resolution mass spectrum calcd for C₁₀H₁₂O₃+Na: 203.068. Found: 203.072. Melting point = 77 °C.

4,5-Bis(methoxymethyl)cyclohex-4-ene cis-1,2-dicarboxylic anhydride (Anhydride V). 2,3-Bis(methoxymethyl)-1,3-butadiene was synthesized as previously reported.²⁴ The diene was combined with a solution of maleic anhydride in toluene and refluxed for one hour. The solvent was evaporated to isolate the crude product, which was purified by recrystallization

from chloroform in 65 % yield. ^1H NMR (400 MHz, *acetone-d*₆) δ ppm 3.97 (dd, J = 60.9, 11.7 Hz, 4H), 3.65-3.57 (m, 2H), 3.21 (s, 6H), 2.69-2.37 (m, 4H). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 173.90 (-CO₂-), 133.58 (=C-CH₂-OCH₃), 70.37 (-CH₂-OCH₃), 58.14 (-OCH₃), 40.07 (-CH-CO₂-), 26.91 (-CH₂-CH-CO₂-). High resolution mass spectrum calcd for C₁₂H₁₆O₅+Na: 263.090. Found: 263.088. Melting point = 94 °C.

Polymer Synthesis. A 10 mL round bottom flask was charged with dicarboxylic acid or anhydride (1.0 equiv) and 1,8-octanediol (1.0 equiv). The flask was sealed with a rubber septum, evacuated, and refilled with argon gas. A homogenous melt was formed by heating the flask to 160 °C with magnetic stirring. Tin octanoate (0.01 equiv) was added to the melt. The reaction mixture was allowed to stir for 1h, and then the pressure was reduced to 30 mmHg and stirred for 23 additional hours (24h total reaction time). At this time, the reaction mixture was allowed to cool and dissolved in chloroform. This solution was precipitated into stirring methanol at -78 °C. Methanol was decanted from the polymer, and the oil was dried in a vacuum oven at 50 °C for 24h. For each reaction, approximately 500 – 1000 mg of diacid or anhydride was used.

Poly(octanediol 5-norbornene-trans-2,3-dicarboxylate). ^1H NMR (400 MHz, CDCl_3) δ ppm 6.15 (ddd, J = 92.0, 5.5, 2.9 Hz, 2H), 4.14-3.93 (m, 4H), 3.36 (t, J = 4.1, 4.1 Hz, 1H), 3.17 (d, J = 59.5 Hz, 2H), 2.66 (dd, J = 4.3, 1.4 Hz, 1H), 1.66-1.57 (m, 5H), 1.51-1.40 (m, 1H), 1.31 (s, 8H). ^{13}C NMR (100.61 MHz, CDCl_3) δ ppm 174.42 (-CO₂-), 173.25 (-CO₂-), 137.53 (=CH-), 134.98 (=CH-), 64.57 (-CO₂-CH₂-), 47.82 (-CHCO₂-), 47.71 (-CHCO₂-), 47.22 (-CHC=), 47.14(-CHC=), 45.65 (bridgehead), 29.03 (-OCH₂CH₂CH₂-CH₂-), 28.53 (-OCH₂CH₂-), 25.76 (-OCH₂CH₂-CH₂-).

Poly(octanediol 5-norbornene-cis-2,3-dicarboxylate). ^1H NMR (400 MHz, CDCl_3) δ ppm 6.22 (s, 2H), 4.11-3.82 (m, 4H), 3.25 (s, 2H), 3.13 (s, 2H), 1.64-1.50 (m, 5H), 1.47-1.42 (m, 1H), 1.29 (s, 8H). ^{13}C NMR (100.61 MHz, CDCl_3) δ ppm 172.41 (-CO₂-), 134.77 (=CH-), 64.37 (-CO₂-CH₂-), 48.59 (-CHCO₂-), 48.11 (-CHC=), 46.28 (bridgehead), 29.08 (-OCH₂CH₂CH₂-CH₂-), 28.44 (-OCH₂CH₂-), 25.82 (-OCH₂CH₂-CH₂-).

Poly(octanediol 4-methylcyclohex-4-ene-trans-1,2-dicarboxylate). ^1H NMR (400 MHz, CDCl_3) δ ppm 5.36 (s, 1H), 4.16-3.95 (m, 4H), 2.80 (dtd, J = 37.0, 10.7, 10.7, 5.6 Hz, 2H), 2.46-2.00 (m, 4H), 1.65 (s, 3H), 1.59 (s, 4H), 1.29 (s, 8H). ^{13}C NMR (100.61 MHz, CDCl_3) δ ppm 174.87 (-CO₂-), 174.74 (-CO₂-), 132.03 (=C(CH₃)-), 118.81 (=CH-), 64.48 (-CO₂-CH₂-), 41.54 (-CHCO₂-), 40.96 (-CHCO₂-), 32.36 (-OCH₂CH₂CH₂-CH₂-), 28.92 (-OCH₂-CH₂-), 28.35 (-OCH₂CH₂-CH₂-), 27.93 (-CH₂-CH=), 25.58 (-CH₂-C(CH₃)-), 22.85 (-CH₃).

Poly(octanediol 4-methylcyclohex-4-ene-cis-1,2-dicarboxylate). ^1H NMR (400 MHz, CDCl_3) δ ppm 5.34 (s, 1H), 4.16-3.95 (m, 4H), 2.98 (dtd, J = 9.8, 6.3, 6.2, 3.6 Hz, 2H), 2.40 (dddt, J = 45.3, 45.3, 23.3, 11.4, 3.5 Hz, 4H), 1.65 (s, 3H), 1.58 (m, 4H), 1.29 (s, 8H). ^{13}C NMR (100.61 MHz, CDCl_3) δ ppm 173.32 (-CO₂-), 173.28 (-CO₂-), 132.39 (=C(CH₃)-), 119.04 (=CH-), 64.56 (-CO₂-CH₂-), 40.24 (-CHCO₂-), 39.52 (-CHCO₂-), 30.38 (-OCH₂CH₂CH₂-CH₂-), 29.08 (-OCH₂-CH₂-), 28.48 (-OCH₂CH₂-CH₂-), 25.95 (-CH₂-CH=), 25.79 (-CH₂-C(CH₃)-), 23.36 (-CH₃). Anal. Calcd for CHO: C, 69.36; H, 8.90; O, 21.74. Found: C, 67.71; H, 8.72; O, 22.30.

Poly(octanediol 4,5-dimethylcyclohex-4-ene-trans-1,2-dicarboxylate). ^1H NMR (400 MHz, CDCl_3) δ ppm 4.23-3.90 (m, 4H), 2.85-2.73 (m, 2H), 2.30-2.00 (m, 4H), 1.60 (s, 10H), 1.29 (s, 8H). ^{13}C NMR (100.61 MHz, CDCl_3) δ ppm 174.79 (-CO₂-), 123.69 (=C(CH₃)-),

64.41 (-CO₂-CH₂-), 41.84 (-CHCO₂-), 33.97 (-CH₂-CHCO₂-), 28.94 (-OCH₂CH₂CH₂-CH₂-), 28.37 (-OCH₂-CH₂-), 25.59 (-OCH₂CH₂-CH₂-), 18.42 (-CH₃). Anal. Calcd for C₁₈H₂₈O₄: C, 70.10; H, 9.15; O, 20.75. Found: C, 68.72; H, 9.19; O, 21.53.

Poly(octanediol 4,5-dimethylcyclohex-4-ene-cis-1,2-dicarboxylate). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.10-3.96 (m, 4H), 2.96 (t, *J* = 5.1, 5.1 Hz, 2H), 2.32 (ddd, *J* = 76.0, 16.1, 3.3 Hz, 4H), 1.67-1.47 (m, 10H), 1.28 (s, 8H). ¹³C NMR (100.61 MHz, CDCl₃) δ ppm 173.36 (-CO₂-), 123.84 (=C(CH₃)-), 64.48 (-CO₂-CH₂-), 40.39 (-CHCO₂-), 31.84 (-CH₂-CHCO₂-), 29.10 (-OCH₂CH₂CH₂-CH₂-), 28.48 (-OCH₂-CH₂-), 25.78 (-OCH₂CH₂-CH₂-), 18.84 (-CH₃). Anal. Calcd for C₁₈H₂₈O₄: C, 70.10; H, 9.15; O, 20.75. Found: C, 67.91; H, 8.91; O, 22.12.

Poly(octanediol 4,5-bis(methoxymethyl)cyclohex-4-ene-cis-1,2-dicarboxylate). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.04 (t, *J* = 6.8, 6.8 Hz, 4H), 3.93 (dd, *J* = 45.2, 11.4 Hz, 4H), 3.25 (s, 6H), 3.01 (t, *J* = 5.3, 5.3 Hz, 2H), 2.68-2.39 (m, 4H), 1.67-1.50 (m, 4H), 1.28 (s, 8H). ¹³C NMR (100.61 MHz, CDCl₃) δ ppm 172.99 (-CO₂-), 130.94 (=CCH₂OCH₃), 71.01 (-CH₂OCH₃), 64.73 (-CO₂-CH₂-), 57.69 (-OCH₃), 39.83 (-CHCO₂-), 29.15 (-OCH₂CH₂CH₂-CH₂-), 28.51 (-OCH₂-CH₂-), 28.41 (-OCH₂CH₂-CH₂-), 25.84 (-CH₂-CHCO₂-). Anal. Calcd for C₂₀H₃₂O₆: C, 65.19; H, 8.75; O, 26.05. Found: C, 61.56; H, 8.23; O, 26.00.

Copolymer Synthesis. Copolymers were synthesized as above, varying the feed of the diacids to maintain stoichiometry with 1,8-octanediol. All copolymerizations were run for 24h.

Poly(octanediol 4,5-dimethylcyclohex-4-ene-trans-1,2-dicarboxylate-co-octanediol 4-(N,N-diethylaminomethyl)cyclohex-4-ene-trans-1,2-dicarboxylate). ¹H and ¹³C NMR data

are given for the copolymer formed from the reaction of an equimolar amount of the two diacids. ^1H NMR data in the series of copolymers varies only by the integration area for peaks corresponding to protons in the diacid portion of the molecule. ^1H NMR (300 MHz, CDCl_3) δ ppm 5.54 (s, 1H), 4.23-3.91 (m, 8H), 2.87 (s, 2H), 2.85-2.70 (m, 4H), 2.41 (dd, J = 7.3, 3.0 Hz, 6H), 2.15 (ddd, J = 19.9, 9.2, 3.5 Hz, 4H), 1.59 (s, 14H), 1.28 (s, 16H), 0.95 (t, J = 7.1, 7.1 Hz, 6H). ^{13}C NMR (100.61 MHz, CDCl_3) δ ppm 174.87 (-CO₂-), 173.32 (-CO₂-, amine), 123.81 (=C-CH₂-N), 123.77 (=C-CH₃), 109.49 (=C-H), 64.51 (-CO₂-CH₂-), 59.59 (=C-CH₂-N), 46.35 (N-CH₂CH₃), 41.93 (-CHCO₂-), 40.34 (-CHCO₂-), 34.07 (-CH₂-CHCO₂-), 31.81 (-CH₂-CHCO₂-), 29.04 (-OCH₂CH₂CH₂-CH₂-), 28.47 (-OCH₂-CH₂-), 25.70 (-OCH₂CH₂-CH₂-), 18.53 (-CH₃), 11.37 (NCH₂CH₃). Elemental analysis is listed by the amount of amine-containing diacid used to prepare the given polymer (See Table 2.3). Anal. Calcd for 90:10 (C₁₈H₂₈O₄)₉(C₂₁H₃₅O₄N)₁: C, 69.99; H, 9.20; O, 20.43; N, 0.38. Found: C, 68.49; H 9.13; O, 20.82; N, 0.42. Anal. Calcd for 80:20 (C₁₈H₂₈O₄)₈(C₂₁H₃₅O₄N)₂: C, 69.88, H, 9.25; O, 20.10; N, 0.77. Found: C, 68.96; H, 9.28; O, 20.65; N, 0.84. Anal. Calcd for 70:30 (C₁₈H₂₈O₄)₇(C₂₁H₃₅O₄N)₃: C, 69.77; H, 9.30; O, 19.78; N, 1.15. Found: C, 67.31; H, 9.10; O, 20.55; N, 1.31. Anal. Calcd for 60:40 (C₁₈H₂₈O₄)₆(C₂₁H₃₅O₄N)₄: C, 69.66; H, 9.35; O, 19.45; N, 1.53. Found: C, 66.75; H, 9.10; O, 20.86; N, 1.64. Anal. Calcd for 50:50 (C₁₈H₂₈O₄)₅(C₂₁H₃₅O₄N)₅: C, 69.56; H, 9.40; O, 19.13; N, 1.92. Found: C, 66.21; H, 8.95; O, 20.80; N, 1.88.

Alcohol End-capped Polyester Synthesis. The desired diacid or anhydride (.90 equiv) and 1,8-octanediol (1.0 equiv) were mechanically stirred in a 50 mL pear-shaped flask at 160 °C using magnetic stirring until a homogeneous melt formed. Upon formation, Sn(Oct)₂ (0.01 equiv) was added to the melt. The mixture was stirred for 1h, when the

pressure was reduced to 30 mmHg. After 6h of total reaction time, full vacuum was applied to the system. The reaction was allowed to proceed for a total reaction time of 24h. The polymerization was terminated by dissolving the mixture in chloroform and precipitating the solution into stirring methanol. Reactions were performed on a 5 g scale.

Elastomer Synthesis. Elastomer films were prepared by spreading a mixture of the liquid prepolymer (0.20 g – 2.00 g) and AIBN (5.0 wt. %) in a Teflon mold. The mixture was heated in an oven for 24h at the desired temperature, after which the film was removed. Following removal, it was allowed to cool to room temperature and was removed from the mold.

Characterization. ^1H and ^{13}C NMR spectra were acquired in deuterated chloroform on a Bruker 400 AVANCE spectrometer. Molecular weights, relative to narrow polystyrene standards, were measured using a Waters GPC system using RI detection. The measurements were taken at 35 °C with tetrahydrofuran as the mobile phase on three columns (Waters Styragel HR2, HR4, HR5). Thermal transitions were measured with a Seiko 220C DSC on the second heat with a heating rate of 10 °C/min. Thermogravimetric analysis was carried out using a Perkin Elmer TGA with a heating rate of 10 °C/min in a N_2 atmosphere. Mass spectra were recorded on a Bruker BioTOF II Reflectron time-of-flight mass spectrometer in high resolution mode using electrospray ionization in the positive mode. Elemental analysis was conducted by Atlantic Microlab, Inc. of Norcross, GA.

Contact Angle Measurement. A 5 wt. % solution of the respective polymers were spin-coated onto a silicon wafer at 7000 rpm for 1 min. Contact angles measurements were performed on a KSV 200 Optical Contact Angle Meter. Water was used as the wetting liquid.

Sol Gel Analysis. Sol-Gel analysis was conducted by swelling a 0.15 g elastomer film in methylene chloride for 24 h at 25 °C. The solvent was removed and the percent soluble fraction (Q_s) was determined according to the following equation,

$$Q_s = \left(\frac{m_i - m_f}{m_i} \right) \times 100$$

where m_i and m_f represent the initial and final mass. Each measurement was performed on three separate samples. The value was reported as the average of the three measurements.

Mechanical Analysis. Elastomers for mechanical testing were synthesized by placing the prepolymer mixture in a dogbone-shaped Teflon mold with a test area 10 mm long, 3 mm wide and 1.5 mm thick. The mixture was cured as above. Mechanical data were collected on an Instron 5566 at a crosshead speed of 10 mm/min (approximately 100 % extension per min) at 25 °C. The Young's modulus (E) was calculated using the initial linear portion of the stress/strain curve (0 – 5 % strain). The crosslinking density ν was calculated according to the following equation,

$$\nu = \frac{E}{3RT}$$

where R represents the universal gas constant and T is the temperature in K. Each measurement was performed on three separate samples. The value was reported as the average of the three measurements.

Cytotoxicity Testing. MicroMed Laboratories (Petaluma, CA) performed all cytotoxicity analysis. Minimum Essential Medium (MEM) elution tests were performed according to the USP <87> standard using L929 mouse fibroblast cells. Elastomer samples (0.20 g) were extracted in serum-supplemented medium (1.0 mL) for 24 h, and the medium was then exposed to confluent monolayers of cells. At the conclusion of 48 h, the cells were

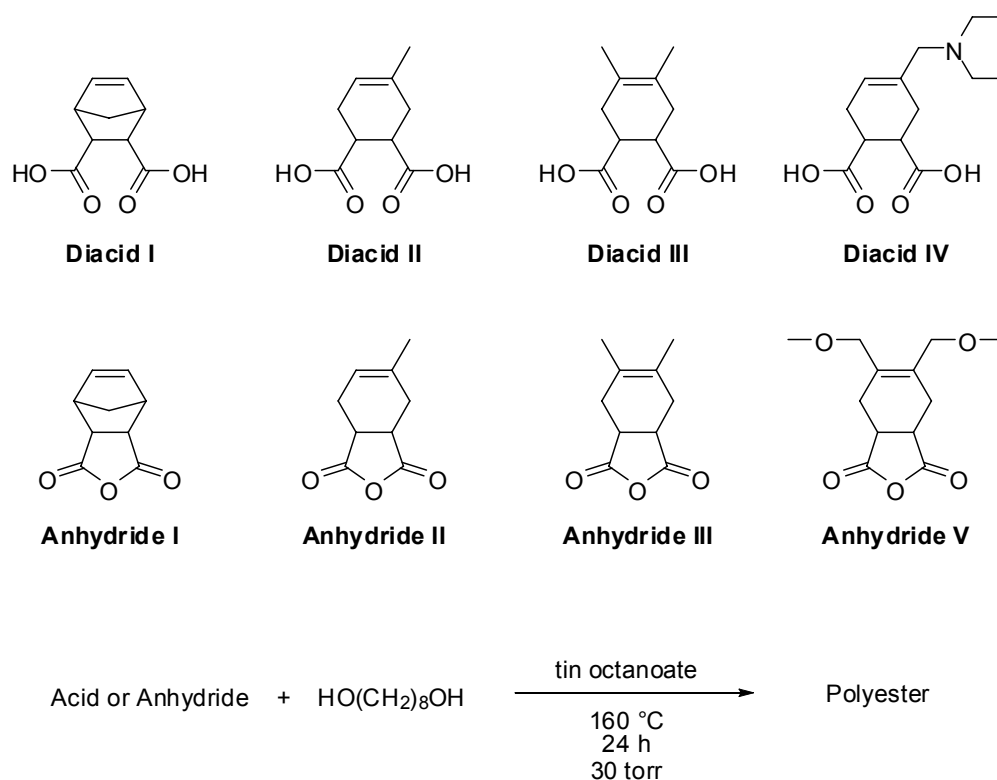
examined by light microscopy, and cytotoxicity was scored on a 0 to 4 scale, 0 being the least cytotoxic. Any material with a score less than or equal to 2 is considered to pass the assay.

2.3 Results and Discussion

Amorphous aliphatic polyesters were designed, synthesized and characterized that have unique solubility, functionality, and thermal properties relative to materials currently available for biomedical applications. The Diels-Alder reaction is the centerpiece of this methodology, as it was used to form new difunctional step growth monomers via the reaction of fumaric acid or maleic anhydride and a variety of dienes. These unsaturated dicarboxylate monomers were incorporated into high molecular weight aliphatic polyesters by step growth polycondensations with alcohols. The amorphous nature of these materials can be ascribed to the bulk of the cyclohexene ring in each repeat unit, which prevents the polymer from packing into crystallites. The Diels-Alder reaction allowed for a wide variety of dienes to be incorporated into the dicarboxylate monomers, and thus into the polyesters.

Monomer Design and Synthesis. A series of unsaturated dicarboxylate monomers was synthesized, including two that include polar functionality, as shown in Scheme 2.3. Several of these compounds (mostly norbornene-based dicarboxylates) have been used for many years in polyester synthesis,¹⁶⁻¹⁸ vinyl polymer synthesis,¹⁹ and ROMP,²⁰ since they contain both an unsaturation and dicarboxylate groups. The Diels-Alder coupling of a diene with either fumaric acid or maleic anhydride was carried out in the absence of Lewis Acid catalyst to prevent the diene from polymerizing by cationic chain-growth polymerization. Using cyclopentadiene as the diene led to polyesters that had a relatively reactive 1,2-disubstituted vinyl group in each repeat unit (Diacid I and Anhydride I). To control the

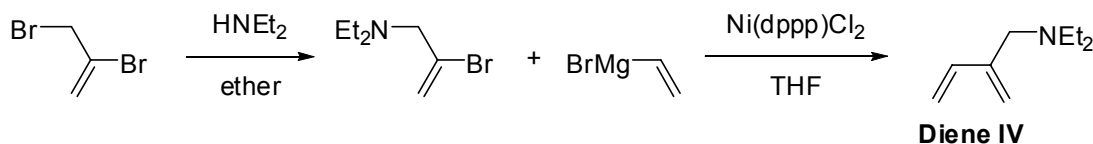
reactivity of the double bond in the polyester backbone, isoprene and 2,3-dimethyl-1,3-butadiene were chosen to yield materials with 1,1,2-trisubstituted (Diacid II and Anhydride II) and 1,1,2,2-tetrasubstituted (Diacid III and Anhydride III) double bonds respectively. These monomers were used to optimize the polymerization conditions and to understand the effect of the monomer structure on the final polymer properties. The information yielded in these studies was applied in the synthesis and polymerization of monomers containing amine and ether functional groups.



Scheme 2.3. Synthetic strategy for preparing new unsaturated aliphatic polyesters

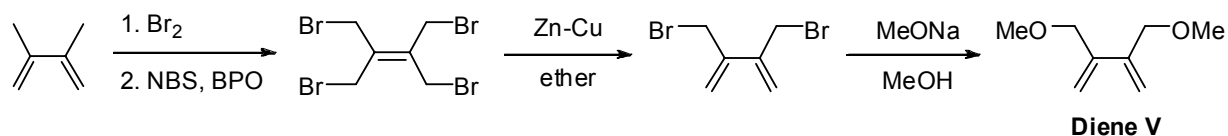
To synthesize monomers with these polar functional groups, dienes with the desired moiety were synthesized. Our group has synthesized a series of amine-functionalized dienes (Scheme 2.4) and polymerized them by chain-growth techniques.²¹⁻²² One of these dienes, 2-

(*N,N*-diethylaminomethyl)-1,3-butadiene (Diene IV), was converted to a step growth monomer by reacting it with fumaric acid to form the dicarboxylic acid (Diacid IV). The amine group was desired because materials containing this functionality have served as gene delivery vectors.²¹



Scheme 2.4. Synthesis of amine-containing Diene IV

We were also interested in synthesizing materials with ether functionality, as side chain ethers have been shown to decrease protein adhesion²³ and alter solubility with respect to their nonpolar counterparts. A methoxy-containing diene, 2,3-bis-methoxymethyl-1,3-butadiene (Diene V), was synthesized using the procedure described by Gaoni (Scheme 2.5).²⁴ The resulting monomer (Anhydride V) contains two side-chain ethers per repeat unit and a relatively unreactive 1,1,2,2-tetrasubstituted double bond. Each Diels-Alder reaction yielded the dicarboxylic monomer in good yield (51 % - 80 %) and in high purity.



Scheme 2.5. Synthesis of ether-functionalized Diene V

Polyester Synthesis. With the monomers in hand, polymerization conditions were studied that rendered materials with high molecular weights. Allowing a dicarboxylate

monomer to react with 1,8-octanediol (OD) in the presence of 1.0 mol % of tin (II) 2-ethylhexanoate (SnOct_2) for 24 h at reduced pressure (30 torr) at 160 °C was found to be the optimal method. The data is summarized in Table 2.1. All materials synthesized had number-average molecular weights of at least $1 \times 10^4 \text{ g mol}^{-1}$ and polydispersity indices of approximately 2.0, as predicted by step growth kinetics. With glass transition temperatures between -30 and -15 °C, all materials were amorphous oils that flowed at room temperature. Polyesters synthesized from the anhydride generally had higher molecular weights than the counterpart that was synthesized from the diacid. This is due to the fact that the anhydride is more reactive in the initial esterification reaction, and because there is only one molecule of water that needs to be removed from the system for each repeat unit. In the diacid case, each repeat unit requires the removal of two equivalents of water. Other advantages of the anhydride approach are that the anhydride monomers were generally easier to purify, had lower melting points, and were easily synthesized by refluxing the diene with maleic anhydride for only one hour. One exception is the case of the norbornene-based monomers and polyesters (Diacid I, Anhydride I, Polyesters 1 and 4). The polymerization of Diacid I was conducted at 130 °C and yielded polyester with a number-average molecular weight of 1.44×10^4 and a polydispersity of 2.0 (Polyester 1). In the case of Anhydride I, polyesterification reactions conducted below 160 °C yielded polymers with molecular weights lower than 1.0×10^4 , while polymerization reactions conducted at 160 °C yielded polymers with broad molecular weight distributions (Polyester 4, $\text{PDI} = 2.7$). This is believed to be due to the steric differences in the mono-ester forms. Upon initial opening of the anhydride, the cis-dicarboxylate is more hindered to a second esterification reaction than the trans-dicarboxylate formed in the diacid case. This may allow for branching side

reactions to dominate at higher temperatures, as discussed below in the copolymerization reactions.

Table 2.1. Polyesters formed from the reaction of the indicated monomer with 1,8-octanediol in the presence of 1 mol % of tin octanoate catalyst for 24h at 160 °C at 30 mmHg

Polyester	Monomer	$\langle M_n \rangle^a$ (g mol ⁻¹)	PDI ^a	T _g ^b (°C)	Weight Loss (°C) ^c		Yield (%)
					5 %	10 %	
1	Diacid I ^d	14 400	2.0	-22	268	289	92
2	Diacid II	17 000	1.7	-20	326	349	96
3	Diacid III	11 500	1.7	-16	318	365	92
4	Anhydride I	13 400	2.7	-21	231	273	92
5	Anhydride II	20 100	1.8	-19	299	339	91
6	Anhydride III	18 300	2.2	-15	351	370	87
7	Anhydride V	16 600	1.9	-26	336	362	93

^a Determined by GPC. ^b Determined by DSC, second heat, 10 °C/min. ^c Determined by TGA in N₂, 10 °C/min. ^d Reaction temperature 130 °C.

Ether-functionalized Polyester Characterization. Particularly notable is the successful synthesis of the side-chain ether containing polyester derived from Anhydride V. The ether functionality was expected to be well tolerated in the reaction conditions, as poly(ester ether) materials have been produced by us under similar conditions.⁸ In this case, each repeat unit contains two equivalents of the polar functionality, which make the polymer more hydrophilic than the corresponding polyester that does not contain these groups. The increased hydrophilicity of the ether-containing polymer (Polyester 7) is evidenced

qualitatively by the differences in solubility between this polymer and the polyester derived from Anhydride III and octanediol (Polyester 6), as shown in Table 2.2.

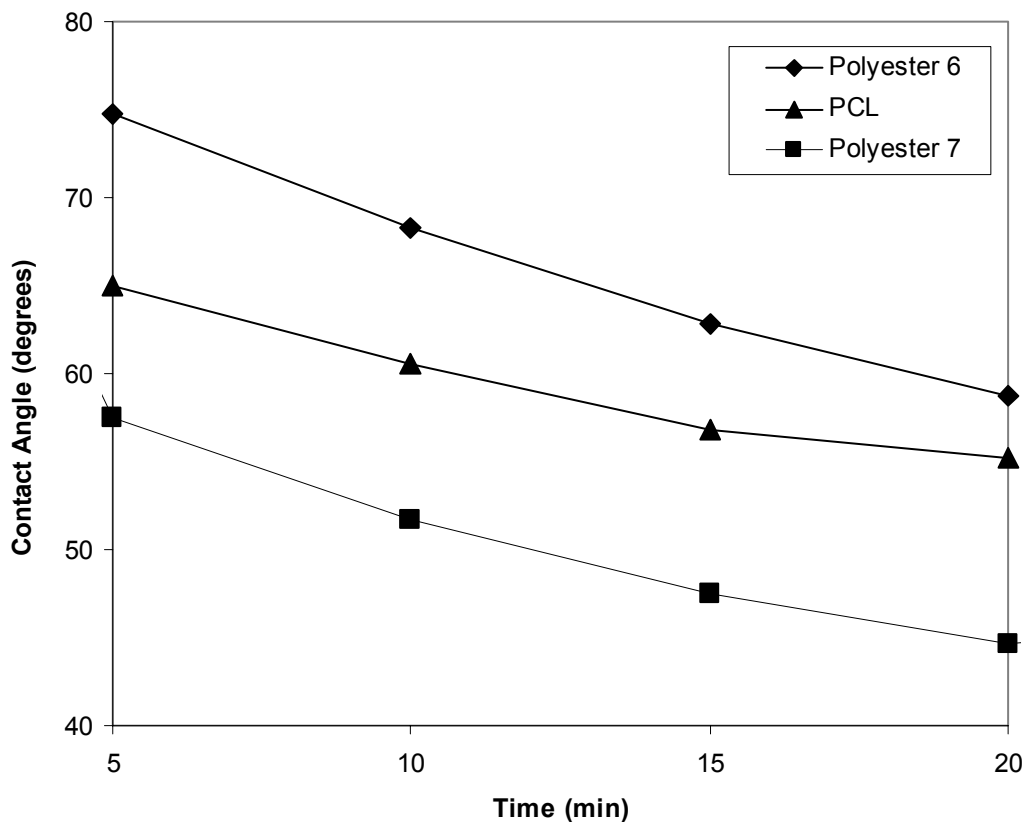
Table 2.2. Solubility characteristics of unsaturated polyester and ether-functionalized unsaturated polyester ^a

Material	water	methanol	acetone	THF	DCM	hexanes
Polyester 6	-	-	=	+	+	-
Polyester 7	-	=	+	+	+	-

^a Symbols: -, insoluble; =, partially soluble; +, freely soluble. ^b 50 mg of polymer in 1 mL of solvent, 25 °C.

Further evidence that the ether groups make the material more hydrophilic is shown by water contact angle data. Uniform films of each of the two materials were spin-coated onto silicon wafers for water contact angle measurements. The initial contact angles were similar (~90°), but over time the water droplet spread across the surface. This behavior is depicted in Figure 2.1, which compares the mean water contact angles as they decrease with time. The water droplet spread very quickly across the ether-containing Polyester 7, stabilizing to a contact angle of about 45° within 15 minutes. The control material, Polyester 6, also showed that the droplet could spread across its surface, but at a slower rate and to a lesser extent. In a control experiment, a commercial sample of poly(ε-caprolactone) (Aldrich, $\langle M_n \rangle = 1.0 \times 10^4$ g/mol, PDI = 1.4) was also analyzed in the same manner. It can be seen that the PCL displayed an intermediate hydrophilicity between the two samples tested. These data show that modifying the polymer structure with two ether groups per repeat unit significantly changes the solubility and hydrophilicity of the material.

Figure 2.1. Comparison of water droplet spreading between unsaturated polyester and ether-functionalized unsaturated polyester



Amine-containing Copolyester Synthesis. Given the successful synthesis of the ether-containing material, attempts were made to synthesize amine-containing polyester in a similar manner. The amine-containing Diacid IV was subjected to the same synthetic conditions as all of the other monomers in an attempt to form amine-containing homopolymers. When the polymerization reaction was attempted at 160 °C, the reaction product did not dissolve in chloroform; rather it swelled in the solvent, an indication that a crosslinked material was produced. If the reaction temperature was lowered to 130 °C, only oligomers were isolated. In order to incorporate Diacid IV into polyesters, a series of

copolymerizations with Diacid III and octanediol was carried out. All mixtures were polymerized at 160 °C for 24h in the presence of tin octanoate (1 mol %). The feed ratio of Diacid III to Diacid IV was studied in increasing increments of 10 %, as shown in Table 2.3.

Table 2.3. Polyesters formed from the reaction of the indicated monomers with 1,8-octanediol in the presence of 1 mol % of tin octanoate catalyst for 24h at 160 °C at 30 mmHg

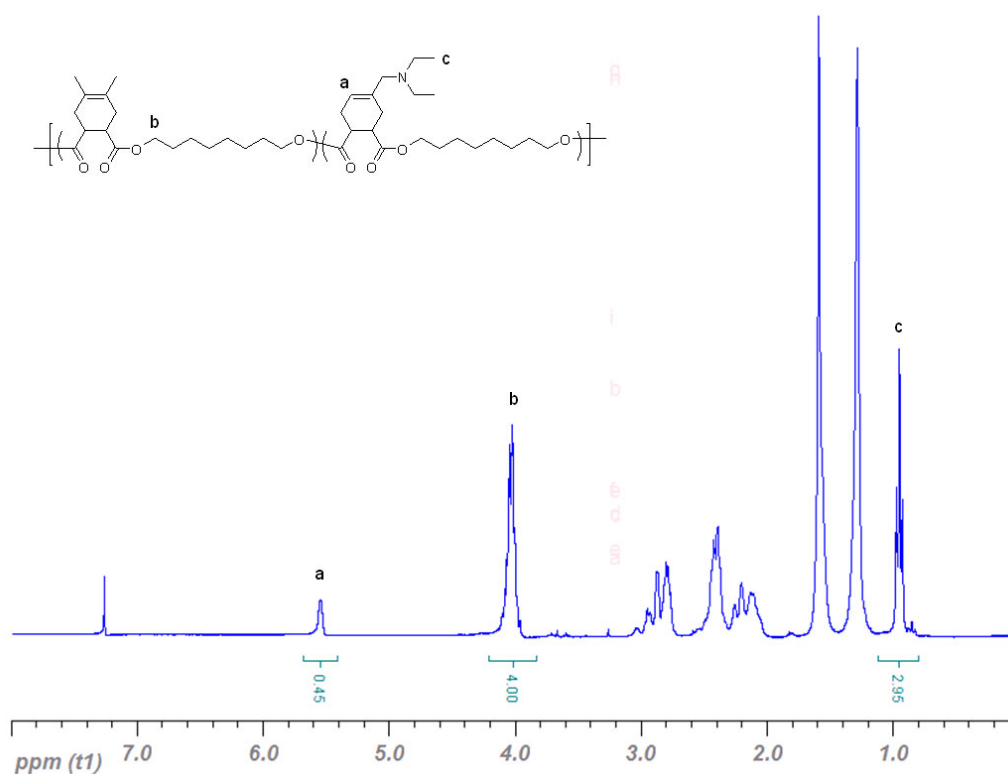
Feed Ratio of Diacid III : IV	Polymer Composition ^a	Mol % of Vinyl Proton ^a	$\langle M_n \rangle$ ^b (g mol ⁻¹)	PDI ^b	T _g ^c (°C)	Yield (%)
90 : 10	90 : 10	7	11 400	1.9	-19	89
80 : 20	81 : 19	18	15 000	2.1	-21	88
70 : 30	73 : 27	27	16 200	3.3	-28	94
60 : 40	60 : 40	37	12 000	2.1	-26	90
50 : 50	51 : 49	45	18 400	3.2	-28	75

^a Determined by ¹H NMR. ^b Determined by GPC. ^c Determined by DSC, second heat, 10 °C/min.

The amount of amine monomer that was incorporated in the copolyesters was determined by integrating the peak for the methyl group (-NCH₂CH₃, 0.95 ppm, peak c) and the peak for the methylene protons adjacent to the ester group (-CO₂-CH₂-, 4.02 ppm, peak b) in the ¹H NMR spectra of the polymers (Figure 2.2). The amount of amine monomer in the feed correlated well to the amount incorporated in the polymer. However, the integration of the vinyl peak (5.54 ppm, Peak A) showed some discrepancies that indicated that amine was incorporated into the polyesters, but that some of the double bonds had been consumed. The molecular weights of all of the materials were in the range of 1.0 – 2.0 x 10⁴ g mol⁻¹, but as the amount of amine monomer in the feed is increased, the molecular weights and

polydispersities of the resulting copolymers generally increased, which indicates some degree of uncontrolled branching in the reaction. Also, in the case of the 50 : 50 copolymer, a low yield resulted due to some intractable material left in the reaction vessel. At higher loadings, completely insoluble crosslinked gels resulted.

Figure 2.2. ^1H NMR spectra of Copolymer 5, 50 : 50 feed ratio of Diacid III : IV



These observations may likely be explained by analogy to the Ordelt reaction, which has been studied in the synthesis of unsaturated polyester resins from diol maleates or fumarates.²⁵⁻²⁸ This reaction involves the addition of an alcohol across the double bond of the dicarboxylate. This leads to a branch point and an increase in molecular weight and

polydispersity. Experiments are underway to further understand the exact nature of the branching and crosslinking in the Diels-Alder system in an effort to synthesize amine-containing polyesters in a well-controlled manner.

Elastomer Synthesis and Characterization. All of the materials synthesized feature a double bond in each repeat unit and are amorphous liquids that flow at room temperature, which make them suitable candidates as thermoplastic precursors to polyester elastomers. As shown previously⁸, when a liquid, unsaturated polyester is reacted with a radical initiator, a degradable amorphous elastomer results. In the crosslinking of the Diels-Alder based materials, it was anticipated that the polyester with di-substituted double bonds (Polyester 1 or 4) would be more reactive towards crosslinking than the tri- or tetra-substituted materials (Polyester 2, 3, 5, or 6). This was tested by thermally crosslinking the materials under the same conditions. To facilitate ease of processing, low molecular weight prepolymers were synthesized by condensing Anhydrides I – III with an excess of octanediol. The stoichiometric imbalance led to materials with lower $\langle M_n \rangle$ ($3.0 - 5.0 \times 10^3 \text{ g mol}^{-1}$), lower T_g (-40 to -30 °C), and 100 % hydroxyl end-groups. Each polyester was mixed with 5 wt. % AIBN and heated at 130 °C for 24h. The resulting elastomers were swollen in methylene chloride for 24h to find the soluble fraction (Q_s) as an indication of the reactivity of the olefins towards the crosslinking reaction. The results follow the expected trend (Table 2.4). The fully substituted olefins are not reactive under the conditions studied (Elastomer A), while the tri-substituted material showed moderate reactivity (Elastomer B). The norbornene-based polyester was the most reactive and formed the elastomers with the lowest sol fraction (Elastomer C).

Table 2.4. Sol-gel data for elastomeric materials

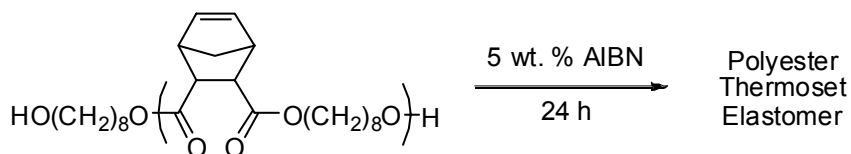
Elastomer	Prepolymer ^a	R ^b	R' ^b	Q_s (%) ^c
A	Polyester 4	H	H	51
B	Polyester 5	H	Me	58
C	Polyester 6	Me	Me	100

^a Polymer listed was combined with 5 wt. % of AIBN and cured for 24h at 130 °C.

^b Substituents at the 4- and 5- positions of the cyclohexene ring. ^c Extracted in methylene chloride for 24 h at 25 °C.

The elastomer that resulted from the crosslinking of Polyester 4 was then evaluated further for its mechanical properties. To vary the mechanical properties of the material, a series of crosslinking reactions were conducted at different temperatures. The resulting materials showed a broad range of properties, as shown in Table 2.5. Elastomer C was a very soft material, as shown by its low Young's modulus value (0.05 MPa) and its ability to stretch to nearly 200 % its original length before failure. Elastomer D was an intermediate material synthesized at 145 °C was slightly stiffer (E = 0.44 MPa) with good ultimate strain (ϵ = 161 %). A much stiffer material was synthesized at 160 °C (Elastomer E, Young's modulus = 11.5 MPa, ϵ = 87 %).

Table 2.5. Properties of elastomers formed by thermal crosslinking of Polyester 4 for 24h using 5 wt % AIBN at the given temperature



Elastomer	T_{cure} (°C)	T_g^a (°C)	Weight Loss (°C) ^b		E^c (MPa)	σ^c (MPa)	ϵ^c (%)	ν^c (mmol/L)	Q_s^d (%)
			5 %	10 %					
C	130	-16	243	264	0.05	0.08	195	7.0	51
D	145	-12	263	288	0.4	0.4	161	60.4	41
E	160	-15	266	291	11.5	1.5	87	1560	27

^a Determined by DSC, second heat, 10 °C/min. ^b Determined by TGA in N₂, 10 °C/min.

^c Determined by Instron, 10 mm/min crosshead speed. ^d Extracted in methylene chloride for 24 h at 25 °C.

Given the high sol content of the materials, the mechanical properties were measured for the insoluble portion that remained after the neat materials were extracted with methylene chloride for 24h at 25 °C (sol-removed samples). In general, these elastomers were more brittle than their precursors, so much so that the sample crosslinked at 130 °C was too brittle to test. The samples crosslinked at 145 °C and 160 °C each had higher Young's moduli, similar ultimate strain, and lower ultimate stress values than the neat elastomers (Table 2.6). This is expected, since the removal of the soluble portion will increase the overall crosslink density, which gives a higher Young's modulus. The high sol content of these elastomers must also be considered in the processing and degradation of these materials, and may be a limitation to the utility of these materials. Further crosslinking methods, such as (meth)acrylate end capping the polyols, may be explored to yield materials with a lower sol content and better mechanical properties.

Table 2.6. Properties of sol-removed elastomers

Elastomer	T _{cure} (°C)	T _g ^a (°C)	Weight Loss (°C) ^b		E ^c (MPa)	σ ^c (MPa)	ϵ ^c (%)	ν ^c (mmol/L)
			5 %	10 %				
C ^d	130	-16	242	266	-	-	-	-
D ^d	145	-14	260	283	1.1	0.4	105	149
E ^d	160	-14	262	292	40.6	2.1	12	5510

^a Determined by DSC, second heat, 10 °C/min. ^b Determined by TGA in N₂, 10 °C/min.

^c Determined by Instron, 10 mm/min crosshead speed. ^d Extracted in methylene chloride for 24 h at 25 °C. ^d Extracted in methylene chloride for 24 h at 25 °C.

Since these materials are intended for biomedical applications, each of the cured elastomers was screened for cytotoxic response according to the current USP <87> standard. The neat elastomers and the sol-removed samples were both subjected to the assay. Each material was extracted with minimum essential medium for 24h, at which point the medium was then added to a confluent monolayer of L-929 mouse fibroblast cells. After incubation for 48h, the cells were visually graded for cell morphology and monolayer confluence. Under the guidelines of this test, a grade of 0 indicates a non-cytotoxic material, a grade of 4 indicates a severely cytotoxic material, and a grade of 2 or less indicates a material that passes the assay. As Table 2.7 indicates, all of the materials were not cytotoxic, with the exception of Elastomer C. This material is the most lightly crosslinked and leaches a larger amount of oligomeric materials, which contribute to the high toxicity. If this material is extracted in methylene chloride before being subjected to the cytotoxicity assay and the oligomers are separated from the elastomer, then the toxicity is eliminated.

Table 2.7. Cytotoxicity results of elastomers formed by thermal crosslinking

Material Tested	Cytotoxicity Grade ^a
Elastomer C	4
Elastomer D	0
Elastomer E	0
Elastomer C ^b	0
Elastomer D ^b	0
Elastomer E ^b	0
Negative Control - HDPE	0
Reagent Control - Medium	0
Positive Controls – High [Salt]	4

^a According to USP <87> standard. ^b Extracted in methylene chloride for 24 h at 25 °C.

2.4 Conclusions

We have introduced a new monomer family based on cyclohex-4-ene 1,2-dicarboxylates synthesized from Diels-Alder chemistry that permit a variety of functional groups in good yields. Subsequent polymerization of these novel monomers was achieved under step growth conditions to yield high molecular weight amorphous polyesters. The thermal crosslinking of these materials allowed for the creation of degradable nontoxic elastomers. The scope of this method includes, but is not limited to, variation in the diene to yield new functionalized dicarboxylate monomers, incorporation of different diols or co-diols in the polyester synthesis, and variation of the crosslinking strategies to yield materials with an even wider range of mechanical properties. This new approach should allow for the solubility, mechanical properties, thermal properties, and topology of polyester materials to

be designed and evaluated in a controlled manner as a means to study aliphatic polyesters intended for biomedical applications.

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2.5 References

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Chapter 3

EVALUATION OF AMINE-CONTAINING POLYESTERS AS GENE DELIVERY VECTORS SYNTHESIZED USING “CLICK” CHEMISTRY

3.1 Introduction

Gene delivery vectors based on synthetic polymers have been studied as potential therapeutics expected to have lower immunogenicity and oncogenicity than viral systems. Amine-containing polymers have been investigated in great detail, as the amine groups can electrostatically associate to the phosphate backbone of DNA, condense the macromolecule and protect it during delivery. The most widely-studied nonviral vector is poly(ethylene imine) (PEI), which can be synthesized in either linear or branched forms. This vehicle has been found to have moderate to high toxicity, and new materials are desired that would be able to deliver DNA as efficiently as PEI but with reduced toxicity.¹

Gene delivery polymers must perform many tasks in order to be successful: they must protect the DNA from degradation, enhance cell binding and endocytosis, facilitate endosomal release, and be nontoxic.² In order to fulfill all of these tasks, synthetic methodologies are required that allow access to well-defined amine-containing polymer compositions and architectures. To decrease toxicity, hydrolytically degradable polymers are desired. Two key strategies have emerged that allow for the precise synthesis of degradable amine-containing polymers: Michael addition and click chemistry.

Langer and coworkers have pioneered studies in the gene delivery capabilities of poly(β -amino esters) formed via the conjugate addition of amines to diacrylates.^{3, 4} Using automated combinatorial techniques, a large variety of amine-containing polymers were synthesized and characterized.⁵⁻⁷ This step-growth polymerization has allowed for the systematic study of molecular weight and end group effects by simple variation of reactant stoichiometry.⁸⁻¹⁰ The combinatorial assays have shown that several features are common among effective vectors, including hydrophobic diacrylates, alcohol- or imidazole-containing side-groups, secondary diamines, amine end groups, and a preference for higher molecular

weights. The best poly(β -amino ester)s were found to have very low toxicity and high transfection efficiency *in vitro* and *in vivo* (via intratumoral injection).¹¹

Another synthetic methodology that enables the synthesis of polymers with well-defined functionality and structure is the copper (I) catalyzed [3+2] cycloaddition of terminal alkynes and azides, which has been characterized as one of the click reactions.^{12, 13} This reaction proceeds in high selectivity to high conversion at mild temperatures in a short time, and it has found widespread use in polymer and dendrimer chemistry.¹⁴⁻¹⁶ The click reaction has recently been applied in the production of a few polymeric gene delivery materials. Reineke used the azide-alkyne coupling reaction to synthesize step-growth polyamides containing trehalose (to enhance biocompatibility) and secondary amines (to bind DNA and enhance cellular uptake).^{17, 18} High molecular weight polymers were formed that bound strongly to DNA, even in the presence of serum. The transfection efficiency and toxicity of these vectors increased as amine content increased¹⁷ and as molecular weight increased.¹⁸ To increase the amine content and to precisely control the size of the delivery vehicles, this group synthesized star-like clusters by grafting oligo(ethyleneimine) arms onto β -cyclodextrin cores with the click reaction.¹⁹ These materials formed DNA polyplexes with controlled sizes and reduced toxicities relative to their linear counterparts. Hennink has employed the click reaction to graft azide-terminated poly[2-(dimethylamino)ethyl methacrylate] arms onto alkyne-modified poly(2-hydroxyethyl methacrylate) backbones.²⁰ Carbonate linkers at the grafting points allowed for the graft copolymers to rapidly degrade to low molecular weight PHEMA and PDMAEMA components. These vectors exhibited high transfection efficiency (similar to high molecular weight polycations), and low toxicity (similar to low molecular weight vectors). These examples demonstrate the utility of the

click reaction in designing gene transfection vectors with precise functionality and architecture.

Fundamental synthetic developments have allowed the click reaction to be applied to aliphatic polyesters as well. Emrick first reported that the click reaction can be applied to pendant alkyne containing polyesters. Azide-terminated PEG and oligopeptides were grafted to the linear polymers without degrading the ester backbone.²¹ This approach was expanded in a later report to include the grafting of camptothecin and PEG onto the polyester to form a water soluble drug-bearing polyester.²² Lecomte also reported the synthesis of azide-containing polyesters that can participate in the click reaction.²³ A wide variety of functional groups were grafted onto these polymers, including tertiary and quaternary amines.^{24, 25} A final example demonstrated the synthesis of propargyl-functionalized glycolide that was polymerized to high molecular weights.²⁶

Taking these advances into consideration, we designed a flexible system to allow the production of a variety of degradable gene transfection vectors with low toxicity. To meet this goal, step-growth polyesterification techniques were employed for their ability to easily incorporate a wide variety of polar and reactive functionality.²⁷⁻³⁰ In order to apply this approach to polyesters that would be compatible with the click reaction, an azide-functionalized diester was synthesized. This monomer was condensed with a variety of diols to form azide-containing polyesters and poly(ester-ether)s. The subsequent coupling of these polyesters with amine-containing alkyne compounds yielded densely grafted polyesters without degradation of the polyester backbone. By simple variation of the structure of amine-containing alkynes, a series of DNA delivery vectors were synthesized to optimize cell viability and transfection efficiency.

3.2 Experimental Section

Materials. All reagents were purchased from Aldrich and used without further purification unless otherwise noted. Tetrahydrofuran was refluxed over sodium and benzophenone and then distilled. Solvents such as methylene chloride, chloroform, and toluene were dried by distillation after stirring the material over calcium hydride. Pure 1,8-octanediol (OD) was obtained by recrystallization from tetrahydrofuran. Diethylene glycol (2EG), triethylene glycol (3EG), and tetraethylene glycol (4EG) were distilled and stored over molecular sieves. Pure diethyl *meso*-2,5-dibromoadipate was obtained by repeated recrystallization from charcoal and ethanol.

Characterization. ^1H and ^{13}C NMR spectra were acquired in deuterated chloroform on a Bruker 400 AVANCE spectrometer. Molecular weights, relative to narrow polystyrene standards, were measured using a Waters GPC system using RI detection. The measurements were taken at 35 °C with tetrahydrofuran as the mobile phase on four columns (Waters Styragel HR5, HR4, HR2, HR0.5). Thermal transitions were measured with a Seiko 220C DSC on the second heat with a heating rate of 10 °C/min. Thermogravimetric analysis was carried out using a Perkin Elmer TGA with a heating rate of 10 °C/min in a N_2 atmosphere. Mass spectra were recorded on a Bruker BioTOF II Reflectron time-of-flight mass spectrometer in high resolution mode using electrospray ionization in the positive mode. Elemental analysis was conducted by Atlantic Microlab, Inc. of Norcross, GA.

Synthesis of monomer and polymers. *Synthesis of diethyl 2,5-diazidoadipate (N_3A).* Diethyl *meso*-2,5-dibromoadipate (19.94 g, 55.3 mmol) was added to a 1000 mL flask and dissolved in 500 mL of *N,N*-dimethyl formamide (DMF). Sodium azide (10.80 g, 166 mmol) was added to the flask and the reaction mixture was stirred at room temperature

for 24 h. After this time, the reaction mixture was cooled in an ice bath and 300 mL of water was added to the mixture and stirred for 30 minutes. This mixture was extracted with diethyl ether three times, and the combined organics were washed with water and dried over magnesium sulfate. The ether solution was concentrated to yield the crude product as a clear, slightly yellow liquid in 99 % yield. The product was distilled in small batches (5 g) as needed through a short path distillation apparatus at reduced pressure (b.p. 135 °C at 0.2 mmHg). The pure product was isolated as a clear, colorless liquid (4.92 g, 89 % recovery). ¹H NMR (400 MHz, CD₂Cl₂) δ ppm 4.23 (q, *J* = 7.2 Hz, 4H, -CO₂CH₂-), 3.93-3.91 (m, 2H, -O₂CCHN₃-), 1.96-1.77 (m, 4H, -CHN₃CH₂-), 1.29 (t, *J* = 7.2 Hz, 6H, -CH₂CH₃). ¹³C NMR (100.61 MHz, CD₂Cl₂) δ (ppm) 169.73 (-CO₂-), 61.90 (-CO₂CH₂-), 61.43 (-O₂CCHN₃-), 27.50 (-CHN₃CH₂-), 13.81 (-CH₂CH₃). High resolution mass spectrum calcd for C₁₀H₁₆O₄N₆ + Na: 307.113 Da. Found: 307.114 Da. Anal. Calcd for C₁₀H₁₆O₄N₆: C, 42.25; H, 5.67; N, 29.56; O, 22.51. Found: C, 42.22; H, 5.70; N, 29.46; O, 22.69.

Synthesis of polyesters. A 25 mL round bottom flask was charged with 1 equiv of diethyl 2,5-diazidoadipate, 1 equiv of diol, and Novozym® 435 resin (10 wt % of the total monomer wt). The flask was evacuated, refilled with argon, and placed in a 80 °C oil bath and allowed to stir for 2 h. The pressure was then slowly reduced to 40 mmHg, and the reaction was allowed to continue at this pressure for 18 h. The pressure was then reduced to 20 mmHg and allowed to stir for a total reaction time of 48 h. After this time, the reaction mixture was diluted with 5 mL of chloroform and the resin were removed by filtration. The diluted melt was precipitated into stirring hexanes. Reactions were performed on a 5 g scale.

Poly(1,8-octanediol 2,5-diazidoadipate). ¹H NMR (400 MHz, CDCl₃••) δ ppm 4.16 (t, *J* = 6.6 Hz, 4H, -CO₂CH₂-), 3.88-3.90 (m, 2H, -O₂CCHN₃-), 1.94-1.78 (m, 4H, -CHN₃CH₂-), 1.65 (m, 4H, -CO₂CH₂CH₂-), 1.314 (s, 8H, -CO₂CH₂CH₂CH₂CH₂-). ¹³C NMR (100.61

MHz, $CDCl_3$) δ (ppm) 169.83 (-CO₂-), 66.02 (-CO₂CH₂-), 61.52 (-CO₂CHN₃-), 28.90 (-CO₂CH₂CH₂CH₂CH₂-), 28.37 (-CO₂CH₂CH₂-), 27.54 (-CHN₃CH₂-), 25.62 (-CO₂CH₂CH₂CH₂-). Anal. Calcd for C₁₄H₂₂N₆O₄: C, 49.70; H, 6.55; N, 24.84; O, 18.91. Found: C, 49.95; H 6.79; N, 24.31; O, 19.13.

Poly(diethylene glycol 2,5-diazidoadipate). ¹H NMR (400 MHz, $CDCl_3$) δ ppm 4.32 (t, J = 4.6 Hz, 4H, -CO₂CH₂-), 3.95-3.96 (m, 2H, -O₂CCHN₃-), 3.70 (t, J = 4.6 Hz, 4H -CO₂CH₂CH₂O-), 1.97-1.79 (m, 4H, -CHN₃CH₂-). ¹³C NMR (100.61 MHz, $CDCl_3$) δ (ppm) 169.75 (-CO₂-), 68.64 (-CO₂CH₂CH₂O-), 64.58 (-CO₂CH₂-), 61.33 (-CO₂CHN₃-), 27.45 (-CHN₃CH₂-). Anal. Calcd for C₁₀H₁₄N₆O₅: C, 40.27; H, 4.73; N, 28.18; O, 26.82. Found: C, 40.38; H, 4.88; N, 27.07; O, 27.45.

Poly(triethylene glycol 2,5-diazidoadipate). ¹H NMR (400 MHz, $CDCl_3$) δ ppm 4.29 (t, J = 4.8 Hz, 4H, -CO₂CH₂-), 3.94-3.89 (m, 2H, -O₂CCHN₃-), 3.67 (t, J = 4.8 Hz, 4H, -CO₂CH₂CH₂O-), 3.59 (s, 4H, -CO₂CH₂CH₂OCH₂-), 1.94-1.76 (m, 4H, -CHN₃CH₂-). ¹³C NMR (100.61 MHz, $CDCl_3$) δ (ppm) 169.78 (-CO₂-), 70.46 (-CO₂CH₂CH₂OCH₂-), 68.72 (-CO₂CH₂CH₂O-), 64.73 (-CO₂CH₂-), 61.31 (-CO₂CHN₃-), 27.47 (-CHN₃CH₂-). Anal. Calcd for C₁₂H₁₈N₆O₆: C, 42.10; H, 5.30; N, 24.55; O, 28.04. Found: C, 42.13; H, 5.68; N, 23.55; O, 29.00.

Poly(tetraethylene glycol 2,5-diazidoadipate). ¹H NMR (400 MHz, $CDCl_3$) δ ppm 4.33 (t, J = 4.6 Hz, 4H, -CO₂CH₂-), 3.97-3.92 (m, 2H, -O₂CCHN₃-), 3.71 (t, J = 4.8 Hz, 4H, -CO₂CH₂CH₂O-), 3.62 (s, 8H, -CO₂CH₂CH₂OCH₂CH₂-), 1.96-1.74 (m, 4H, -CHN₃CH₂-). ¹³C NMR (100.61 MHz, $CDCl_3$) δ (ppm) 169.76 (-CO₂-), 70.46 (-CO₂CH₂CH₂OCH₂CH₂-), 70.42 (-CO₂CH₂CH₂OCH₂-), 68.63 (-CO₂CH₂CH₂O-), 64.74 (-CO₂CH₂-), 61.25 (-CO₂CHN₃-), 27.45 (-CHN₃CH₂-). Anal. Calcd for C₁₄H₂₂N₆O₇: C, 43.52; H, 5.47; N, 21.75; O, 28.99. Found: C, 43.19; H, 6.12; N, 20.30; O, 30.39.

Synthesis of copolymers. A modified version of the homopolymer synthesis was used for the copolymer synthesis, which is illustrated by a procedure for a 10% N₃A copolymer. N₃A (0.5 equiv), diethyl adipate (0.5 equiv), and diol (1 equiv) were added to a 25 mL round bottom flask with a magnetic stir bar. The remainder of the procedure is identical to the homopolymerization procedure. Each reaction was performed on a 5 g scale.

Poly(1,8-octanediol 2,5-diazidoadipate-co-1,8-octanediol adipate). ¹H NMR (400 MHz, CDCl₃) δ ppm 4.20 (t, *J* = 6.8 Hz, 4H, -CHN₃CO₂CH₂-), 4.06 (t, *J* = 6.8 Hz, 4H, -CH₂CO₂CH₂-), 3.94-3.92 (m, 2H, -O₂CCHN₃-), 2.32 (s, 4H, -O₂CCH₂-), 1.98-1.81 (m, 4H, -CHN₃CH₂-), 1.70-1.60 (m, 12H -CO₂CH₂CH₂- and -O₂CCH₂CH₂-), 1.34 (s, 16H, -CO₂CH₂CH₂CH₂CH₂-). ¹³C NMR (100.61 MHz, CDCl₃) δ (ppm) 173.46 (-CO₂-, AA), 169.97 (-CO₂-, N₃A), 66.15 (-CO₂CH₂-, N₃A), 64.46 (-CO₂CH₂-, AA), 61.56 (-CO₂CHN₃-), 33.93 (-O₂CCH₂-), 29.11 (-CO₂CH₂CH₂CH₂CH₂-, N₃A), 29.07 (-CO₂CH₂CH₂CH₂CH₂-, AA), 28.61 (-CO₂CH₂CH₂-, N₃A), 28.48 (-CO₂CH₂CH₂-, AA), 27.64 (-CHN₃CH₂-), 25.85 (-CO₂CH₂CH₂CH₂-, N₃A), 25.75 (-CO₂CH₂CH₂CH₂-, AA), 24.44 (-O₂CCH₂CH₂-). ¹H NMR spectra vary only by the relative integrated peak areas for all copolymers. ¹³C NMR spectra are identical for all copolymers. Elemental analysis is listed by mol percent N₃A in the copolymer. 0 %: Anal. Calcd for (C₁₄H₂₄O₄): C, 65.60; H, 9.44; O, 24.97. Found: C, 65.47; H, 9.56; O, 25.15. 10 %: Anal. Calcd for (C₁₄H₂₂N₆O₄)₁(C₁₄H₂₄O₄)₉: C, 64.01; H, 9.15; N, 2.48; O, 24.36. Found: C, 63.47; H, 9.18; N, 2.77; O, 24.74. 25 %: Anal. Calcd for (C₁₄H₂₂N₆O₄)₁(C₁₄H₂₄O₄)₃: C, 21.63; H, 8.72; N, 6.21; O, 23.46. Found: C, 60.86; H, 8.74; N, 7.29; O, 23.26. 50 %: Anal. Calcd for (C₁₄H₂₂N₆O₄)₁(C₁₄H₂₄O₄)₁: C, 57.65; H, 8.00; N, 12.42; O, 21.94. Found: C, 55.85; H, 7.82; N, 13.52; O, 22.31. 75 %: Anal. Calcd for (C₁₄H₂₂N₆O₄)₃(C₁₄H₂₄O₄)₁: C, 53.68; H, 7.27; N, 18.63; O, 20.43. Found: C, 51.66; H, 7.14; N, 19.01; O, 20.29.

Synthesis of Amine-Containing Alkynes. A typical procedure for the preparation of the amine-containing alkynes follows. Ethyl and propyl derivatives were prepared in methylene chloride.

Propargyl 3-(dimethylamino)propanoate. A 50 mL flask was dried and purged with nitrogen, and 1.0 g (9 mmol) of propargyl acrylate was added by syringe. The flask was cooled in an ice-water bath, and 9 mL of a 2.0 M (18 mmol) solution of dimethyl amine in THF was added by syringe. The mixture was allowed to stir overnight, at which point it was diluted with methylene chloride. The organic solution was washed with 1.0 M NaOH solution and extracted with CH_2Cl_2 . The combined organic extracts were washed with brine, dried with magnesium sulfate, and concentrated. The isolated liquid was distilled at 66 °C/2 mmHg to yield a clear, colorless liquid (0.78 g, 55 % yield). Density = 0.991 g/mL. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.66 (d, J = 1.6 Hz, 2 H, $\text{HCC-CH}_2\text{-O}_2\text{C-}$), 2.59 (t, J = 6.8 Hz, 2 H, $\text{-O}_2\text{C-CH}_2\text{CH}_2\text{N-}$), 2.49 (t, J = 6.8 Hz, 2 H, $\text{-O}_2\text{C-CH}_2\text{-}$), 2.46 (t, J = 1.6 Hz, 1 H, alkyne proton), 2.21 (s, 6 H, $\text{-N(CH}_3)_2$). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 171.57 ($\text{-CO}_2\text{-}$), 77.64 ($\text{H-CC-CH}_2\text{-}$), 74.87 ($\text{H-CC-CH}_2\text{-}$), 54.50 ($\text{HCC-CH}_2\text{-}$), 51.91 ($\text{-O}_2\text{C-CH}_2\text{CH}_2\text{N-}$), 45.21 ($\text{-N(CH}_3)_2$), 32.57 ($\text{-O}_2\text{C-CH}_2\text{CH}_2\text{N-}$). High resolution mass spectrum calcd for $\text{C}_8\text{H}_{13}\text{NO}_2 + \text{H}$: 156.1025 Da. Found: 156.1022 Da. Anal. Calcd for $\text{C}_8\text{H}_{13}\text{NO}_2$: C, 61.91; H, 8.44; N, 9.03; O, 20.62. Found: C, 61.21; H, 8.49; N, 8.86; O, 21.24.

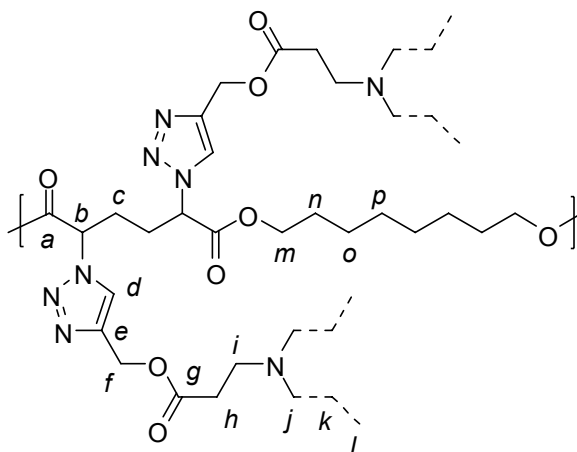
Propargyl 3-(diethylamino)propanoate. The crude material was distilled at 80 °C/2 mmHg to yield 1.12 g (67 % yield). Density = 0.952 g/mL. ^1H NMR (400 MHz, CDCl_3) δ ppm 4.66 (d, J = 2.4 Hz, 2 H, $\text{HCC-CH}_2\text{-O}_2\text{C-}$), 2.79 (t, J = 7.6 Hz, 2 H, $\text{-O}_2\text{C-CH}_2\text{CH}_2\text{N-}$), 2.53 – 2.47 (m, 7 H, overlap: alkyne proton, $\text{-N(CH}_2\text{CH}_3)_2$, $\text{-O}_2\text{C-CH}_2\text{-}$), 1.01 (t, J = 7.2 Hz, $\text{-N(CH}_2\text{CH}_3)_2$). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 171.97 ($\text{-CO}_2\text{-}$), 77.69 ($\text{H-CC-CH}_2\text{-}$), 74.78 ($\text{H-CC-CH}_2\text{-}$), 51.84 ($\text{HCC-CH}_2\text{-}$), 47.89 ($\text{-O}_2\text{C-CH}_2\text{CH}_2\text{N-}$), 46.82 ($\text{-N(CH}_2\text{CH}_3)_2$).

$\text{N}(\text{CH}_2\text{CH}_3)_2$), 32.08 ($-\text{O}_2\text{C}-\text{CH}_2\text{CH}_2\text{N}-$), 11.88 ($-\text{N}(\text{CH}_2\text{CH}_3)_2$). High resolution mass spectrum calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_2 + \text{H}$: 184.1338 Da. Found: 184.1330 Da. Anal. Calcd for $\text{C}_{10}\text{H}_{17}\text{NO}_2$: C, 65.54; H, 9.35; N, 7.64; O, 17.46. Found: C, 60.61; H, 8.73; N, 7.12; O, 17.54.

*Propargyl 3-(di-*n*-propylamino)propanoate.* The crude material was distilled at 94 °C/2 mmHg to yield 1.63 g (85 % yield). Density = 0.907 g/mL. ^1H NMR (400 MHz, CDCl_3)•• δ ppm 4.66 (d, $J = 2.4$ Hz, 2 H, $\text{HCC}-\text{CH}_2-\text{O}_2\text{C}-$), 2.78 (t, $J = 7.2$ Hz, 2 H, $-\text{O}_2\text{C}-\text{CH}_2\text{CH}_2\text{N}-$), 2.49 – 2.46 (m, 3 H, overlap: alkyne proton, $-\text{O}_2\text{C}-\text{CH}_2-$), 2.34 (t, $J = 7.2$ Hz, 4 H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 1.43 (sextet, $J = 7.2$ Hz, 4 H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 0.85 (t, $J = 7.2$ Hz, 6 H, $-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$). ^{13}C NMR (100.61 MHz, CDCl_3 ••••) δ (ppm) 172.01 ($-\text{CO}_2-$), 77.74 ($\text{H}-\text{CC}-\text{CH}_2-$), 74.70 ($\text{H}-\text{CC}-\text{CH}_2-$), 55.95 ($-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 51.76 ($\text{HCC}-\text{CH}_2-$), 49.35 ($-\text{O}_2\text{C}-\text{CH}_2\text{CH}_2\text{N}-$), 32.37 ($-\text{O}_2\text{C}-\text{CH}_2\text{CH}_2\text{N}-$), 20.93 ($-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$), 11.80 ($-\text{N}(\text{CH}_2\text{CH}_2\text{CH}_3)_2$). High resolution mass spectrum calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_2 + \text{H}$: 212.1651 Da. Found: 212.1634 Da. Anal. Calcd for $\text{C}_{12}\text{H}_{21}\text{NO}_2$: C, 68.21; H, 10.02; N, 6.63; O, 15.14. Found: C, 66.30; H, 9.86; N, 6.56; O, 15.61.

Synthesis of Amine-grafted Polyesters. Azide-containing polyester (0.17g, 0.50 mmoles) and copper(I) bromide (14 mg, 0.10 mmoles) were charged into a 10 mL round bottom flask with a stir bar. The flask was evacuated and refilled with nitrogen, and 2 mL of THF were added to dissolve the polymer. After the polymer was dissolved, the appropriate alkyne coupling partner was added by syringe, and the solution was stirred overnight. At this time, the reaction mixture was diluted with methylene chloride and washed with 0.10 M NaOH solution. The water layer was extracted 3 times with methylene chloride, and the combined organic solution was washed with brine, dried with magnesium sulfate,

concentrated, and dried *in vacuo*. NMR spectra follow, and assignments are based on the following structure.



Dimethylamino polyester. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.80 (s, 2 H, proton *d*), 7.76 (s, 1,5-isomer), 5.35 – 5.24 (m, 6 H, protons *b* and *f* overlap), 4.12 (t, $J = 6.0$ Hz, 4 H, proton *m*), 2.63 (t, $J = 6.8$ Hz, 4 H, proton *i*), 2.52 (t, $J = 6.8$ Hz, 4 H, proton *h*), 2.23 (s, 12 H, proton *j*) 2.20 – 1.95 (m, 4 H, protons *c*), 1.56 (s, 4 H, proton *n*), 1.22 (s, 8 H, protons *o* and *p*). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 172.14 (carbon *g*), 167.72 (carbon *a*), 143.45 (carbon *e*), 123.46 (carbon *d*), 66.64 (carbon *b*), 62.06 (carbon *m*), 57.61 (carbon *f*), 54.58 (carbon *i*), 45.15 (carbon *j*), 32.62 (carbon *h*), 28.84 (carbon *p*), 28.45 (carbon *n*), 28.19 (carbon *o*), 25.46 (carbon *c*).

Diethylamino polyester. ^1H NMR (400 MHz, CDCl_3) δ ppm 7.77 (s, 2 H, proton *d*), 7.73 (s, 1,5-isomer), 5.34 – 5.22 (m, 6 H, protons *b* and *f* overlap), 4.12 (t, $J = 6.4$ Hz, 4 H, proton *m*), 2.79 (t, $J = 7.6$ Hz, 4 H, proton *i*), 2.52 – 2.47 (m, 12 H, protons *h* and *j* overlap), 2.25 – 1.96 (m, 4 H, proton *c*), 1.56 (s, 4 H, proton *n*), 1.22 (s, 8 H, protons *o* and *p*), 0.99 (t, $J = 7.2$ Hz, 12 H, proton *k*). ^{13}C NMR (100.61 MHz, CDCl_3) δ (ppm) 172.57 (carbon *g*), 167.70 (carbon *a*), 143.47 (carbon *e*), 123.47 (carbon *d*), 66.64 (carbon *b*), 62.07 (carbon *m*),

57.51 (carbon *f*), 47.98 (carbon *i*), 46.78 (carbon *j*), 32.18 (carbon *h*), 28.85 (carbon *p*), 28.63 (carbon *n*), 28.19 (carbon *o*), 25.45 (carbon *c*), 11.77 (carbon *k*).

Dipropylamino polyester. ^1H NMR (400 MHz, CDCl_3)•• δ ppm 7.78 (s, 2 H, proton *d*), 7.74 (s, 1,5-isomer), 5.33 – 5.22 (m, 6 H, protons *b* and *f* overlap), 4.12 (t, $J = 6.4$ Hz, 4 H, proton *m*), 2.77 (t, $J = 7.2$ Hz, 4 H, proton *i*), 2.46 (t, $J = 7.2$ Hz, 4 H, proton *h*), 2.34 (t, $J = 7.6$ Hz, 8 H, proton *j*), 2.26 – 1.97 (m, 4 H, proton *c*), 1.57 (s, 4 H, proton *n*), 1.40 (sextet, $J = 7.6$ Hz, 8 H, proton *k*), 1.23 (s, 8 H, protons *o* and *p*), 0.85 (t, $J = 7.6$ Hz, 12 H, proton *l*).
 ^{13}C NMR (100.61 MHz, CDCl_3 ••••) δ (ppm) 172.64 (proton *g*), 167.69 (proton *a*), 143.52 (proton *e*), 123.44 (proton *d*), 66.64 (proton *b*), 62.08 (proton *m*), 57.45 (proton *f*), 55.92 (proton *j*), 49.37 (proton *i*), 32.41 (proton *h*), 28.86 (proton *p*), 28.66 (proton *n*), 28.20 (proton *o*), 25.46 (proton *c*), 20.31 (proton *k*), 11.83 (proton *l*).

Titration. Polymer (~30mg) was dissolved in 10 mL of 0.1 M HCl. The solution was then titrated with 0.1 mL aliquots of 0.1 M NaOH while stirring. The pH was recorded after allowing 30 seconds for equilibration. The inflection point of the curve was recorded as the pK_a of the polymer.

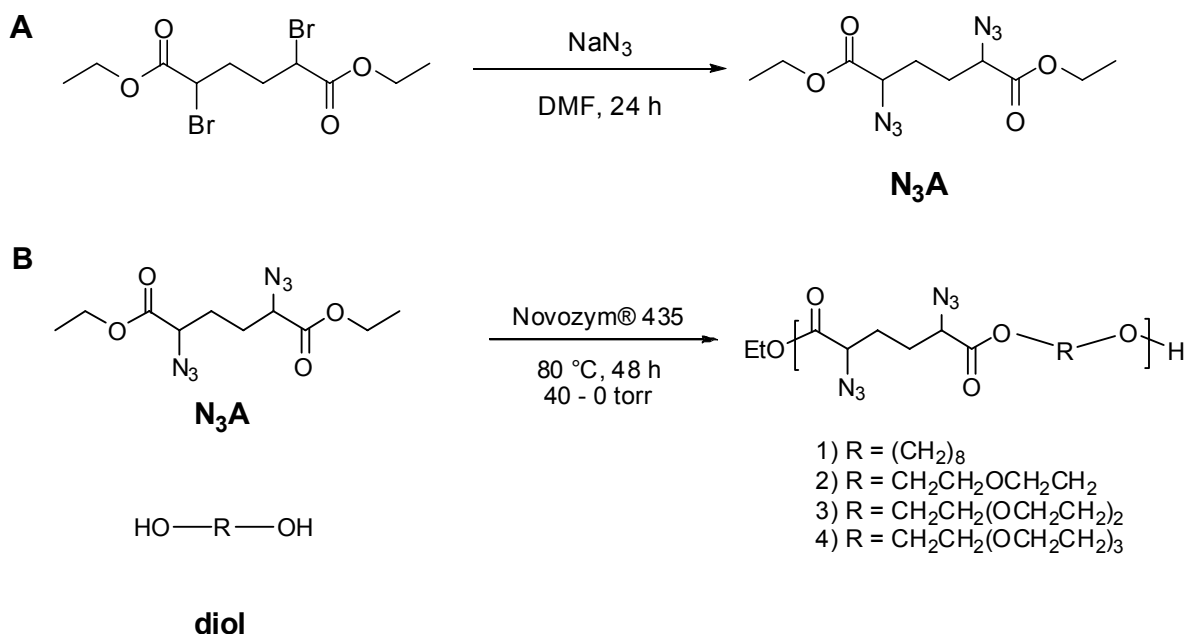
Cytotoxicity Assay. Stock solutions of polymers were made by dissolving 10 mg of polymer into 1 mL of 0.1 M acetic acid. The polymer solutions were then diluted to the appropriate concentrations by reaching a total volume of 10% 0.1 M acetic acid and 90% MEM. HeLa cells were grown in 96-well plates at a density of 1×10^4 cells per well in 150 μL of growth medium (90% MEM, 10% FBS). Cells were grown for 24 h, after which the growth medium was removed. The cells were washed twice with 100 μL of DPBS. A 150 μL aliquot of polymer solution was then added to each well and incubated for 4 h at 37 $^\circ\text{C}$, 5% CO_2 in quintuplicate. The media was then removed, and the cells were washed with

100 μ L of DPBS followed by adding 100 μ L of MEM and 20 μ L of MTS assay (CellTiter 96[®] Aqueous One Solution Cell Proliferation Assay kit). The samples were incubated for 4 h at 37 °C, 5% CO₂. The optical absorbance was measured at 492 nm.

Transfection Assay. Stock solutions of polymers were made by dissolving 2 mg of polymer into 2 mL of 0.1 M acetic acid solution. The polymer solutions were then added to a 1.5 μ L centrifuge tube containing 352 μ L of Opti-MEM, 8.0 μ L of 0.1 μ g/ μ L pCMV-Luc plasmid, and 0.1 M acetic acid, to make solutions with N/P ratios of 10, 20, and 40. The final solutions were 0.4 mL of appropriate DNA to polymer solution with 10% of 0.1 M acetic acid. HeLa cells were grown in 48-well plates at a density of 3×10^4 cells per well in 500 μ L of growth medium (90% MEM, 10% FBS). Cells were grown for 24 h, after which the growth medium was removed. The cells were washed with 200 μ L of DPBS and 300 μ L of Opti-MEM. Polyplex solutions (100 μ L) were added to the cells, and they were incubated for 4 h, 17 °C, 5 % CO₂. The cells were then washed with DPBS, 300 μ L of growth medium was added, and they were incubated for 44 h, 17 °C, 5% CO₂. The growth medium was removed and the cells were washed with 300 μ L of DPBS. The cells were then lysed with 200 μ L of Cell Culture Lysis Buffer (1x), scraped with a pipet tip, and then the lysate was transferred to a 1.5 μ L centrifuge tube. The solutions were centrifuged for 4 min., 12000 g, 4 °C and the supernatant was analyzed by a luciferase assay and BCA protein assay. Transfection efficiency was compared as relative light units (RLU) per μ g of protein.

3.3 Results and Discussion

Monomer Design and Synthesis. An azide-functionalized monomer was designed to be incorporated into polyesters by step-growth condensation. A commercially available precursor, diethyl *meso*-2,5-dibromoadipate, was substituted with sodium azide to yield diethyl 2,5-diazido adipate (N_3A). The azide-containing diester was then distilled under vacuum to yield a clear, colorless liquid in high purity (Scheme 3.1A). During the distillation, the crude material was heated to 160 – 170 °C, and afterwards it became dark in color, indicating thermal degradation. From this observation, it was expected that this material would be sensitive to reaction conditions that required high temperatures for an extended period of time. Several authors have reported previously on the safety concerns of handling azide-containing compounds,¹² and this compound was safely distilled under the conditions described.



Scheme 3.1. Azide-containing monomer and polyester syntheses

Polycondensation of N₃A with Diols. The isolated diethyl 2,5-diazidoadipate monomer was expected to be able to react by two orthogonal pathways. The ester groups allow for the molecule to serve as a monomer for transesterification polymerization, and the azide groups allow for functionalization by the click reaction. Several transesterification conditions were studied and those that required elevated temperatures were unsuccessful. For example, tin octanoate was added to an equimolar mixture of N₃A and 1,8-octanediol (OD), and the reaction mixture was heated to 130 °C under vacuum for 6 h. Under these conditions, the reaction mixture darkened significantly and did not increase in viscosity, indicating decomposition of the monomer. This led us to seek milder reaction conditions. Our group has previously polymerized functionalized adipic acid derivatives with diols in the presence of lipase catalyst at reaction temperatures significantly lower than those needed for metal-catalyzed systems.²⁷ Applying an adapted version of these conditions allowed for the synthesis of high molecular weight polyesters (Scheme 3.1B). One equivalent of N₃A was

combined with one equivalent of OD and heated at 80 °C until a homogeneous melt was formed. Novozym® 435, a commercially available form of *Candida antarctica* lipase B immobilized on acrylate beads, was then added to the flask at a ratio of 10 wt % total monomer weight (1 wt % enzyme). The mixture was stirred and allowed to react at reduced pressure for 48 h. The resulting polymer was isolated in high yield and high molecular weight (Table 3.1). These conditions were then applied to form polymers containing di-, tri-, and tetraethylene glycol repeat units as a means to adjust the hydrophilicity of the resulting polyesters. Each of the polymers was an amorphous liquid at room temperature. Those synthesized from the ether-containing diols were partially methanol-soluble, one indication of their increased polarity over the alkyl equivalent (Table 3.2).

Table 3.1. Properties of azide-functionalized polyesters synthesized by lipase catalysis from N₃A and the listed diol

polyester	diol	$\langle M_n \rangle$ (x 10 ⁻³ g mol ⁻¹) ^a	PDI ^a	T _g (°C) ^b	5 % wt loss (°C) ^c	10 % wt loss (°C) ^c	yield
1	OD	13.0	1.8	-39	223	230	95
2	2EG	4.2	1.6	-25	219	225	86
3	3EG	2.1	1.7	-34	215	224	93
4	4EG	2.3	1.6	-36	218	228	92

^a Determined by GPC. ^b Determined by DSC, second heat, 10 °C/min. ^c Determined by TGA in N₂, 10 °C/min. OD = 1,8-octanediol; 2EG = diethylene glycol; 3EG = triethylene glycol; 4EG = tetraethylene glycol.

Table 3.2. Solubility characteristics of azide-containing polyesters ^a

polyester ^b	water	methanol	acetone	THF	CH ₂ Cl ₂	hexanes
1	-	-	+	+	+	-
2	-	=	+	+	+	-
3	-	=	+	+	+	-
4	-	=	+	+	+	-

^a Symbols: -, insoluble; =, partially soluble; +, freely soluble. ^b 50 mg of polymer in 1 mL of solvent, 25 °C.

Copolymers of N₃A, DEA and OD. In order to modulate the azide content of these materials and to further expand the thermal properties, a series of copolymers were synthesized. Diethyl adipate (DEA) and diethyl 2,5-diazidoadipate were charged in varying ratios with 1,8-octanediol under the polymerization conditions described previously (Scheme 3.2). The set of polyesters were synthesized in high molecular weights with polydispersity indices near 2.0, as predicted for step-growth polymerization (Table 3.3).

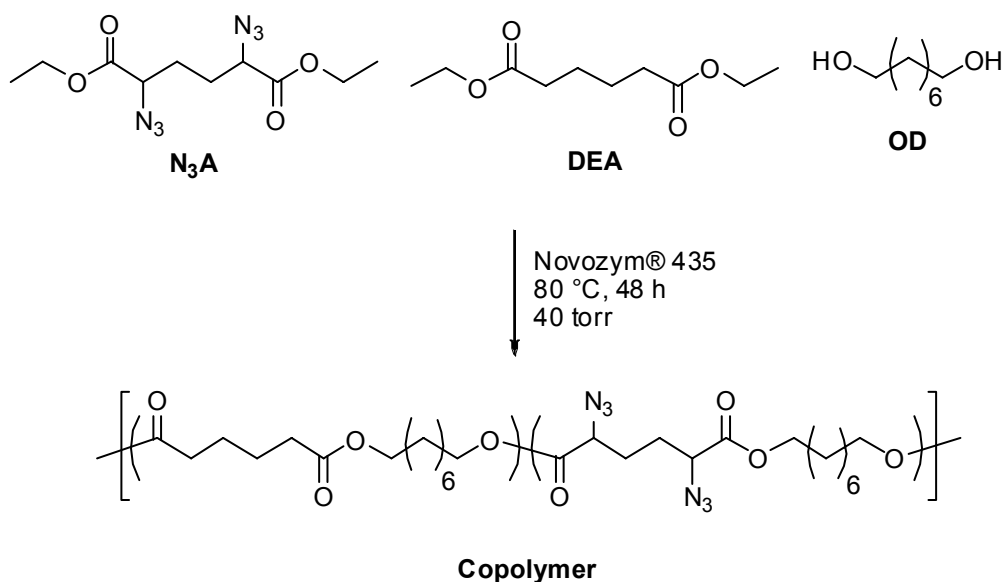
**Scheme 3.2.** Azide-containing copolymer synthesis

Table 3.3. Properties of azide-functionalized copolymers synthesized by lipase catalysis from N₃A and diethyl adipate with 1,8-octanediol

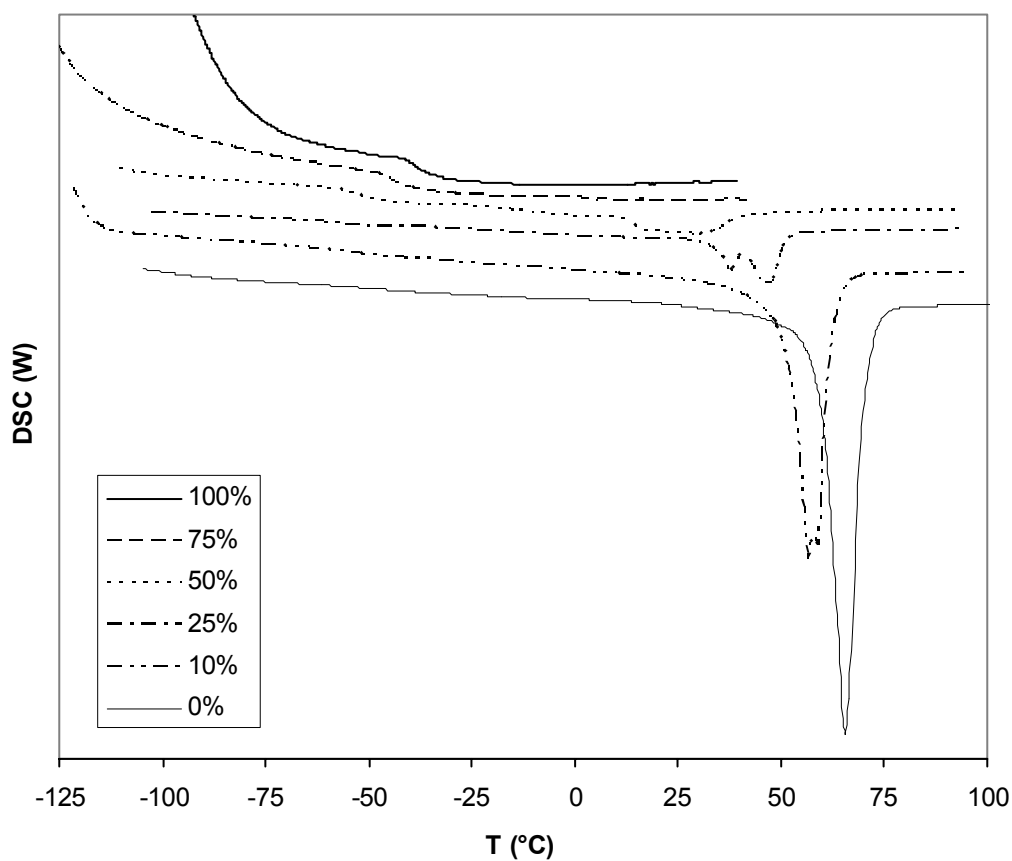
N ₃ A : DEA		$\langle M_n \rangle$		T _g	T _m	ΔH_m	yield
feed	composition ^a	(x 10 ⁻³ g mol ⁻¹) ^b	PDI ^b	(°C) ^c	(°C) ^c	(J/g) ^c	(%)
100 : 0	100 : 0	13.0	1.8	-39	-	-	95
75 : 25	75 : 25	11.3	1.9	-44	5, 10	0.5	89
50 : 50	52 : 48	11.7	1.8	-52	18, 30	15	80
25 : 75	25 : 75	11.3	1.9	-59	38, 47	48	80
10 : 90	9 : 91	16.2	2.3	-	57, 59	106	75
0 : 100	0 : 100	9.0	1.7	-	66	136	85

^a Determined by ¹H NMR. ^b Determined by GPC. ^c Determined by DSC, second heat, 10 °C/min.

The thermal properties of the set of copolymers can be understood based on the characteristics of the two homopolymers. Poly(octyl adipate) is a semicrystalline material with a melting point at 66 °C, while poly(octyl 2,5-diazido adipate) is an amorphous material with a T_g of -39 °C. As more N₃A repeat units are incorporated into the copolymer, the azide side groups are bulky enough to disrupt the crystalline regions, and so both the T_m and the degree of crystallinity decrease (Figure 3.1). Several of the copolymers have two melting points that are very close together. Multiple melting points have been observed in several aliphatic polyesters, including poly(L-lactide),³¹ poly(ε-caprolactone),³² poly(butylene adipate),³³ and poly(ethylene sebacate).³⁴ Two melting points are observed in materials that either have two coexistent crystal structures, a transition from one crystalline structure to another, or a crystalline form that can exhibit two sizes (e.g. two lamellar thicknesses). While we have observed similar dual melting points in previous systems of this type (copolyesters of adipic acid and *trans*-β-hydromuconic acid),²⁷ wide angle X-ray scattering

studies are necessary to determine the cause of the dual melting points. In this case, each material has only one glass transition temperature (where observed), and the T_g increases as the amount of N_3A repeat units increases, as predicted by the Fox equation³⁵ (Figure 3.1). This is expected for copolymers whose repeat units are incorporated randomly. The family of materials presented allows one to select a material with an appropriate amount of azide groups and desired thermal properties.

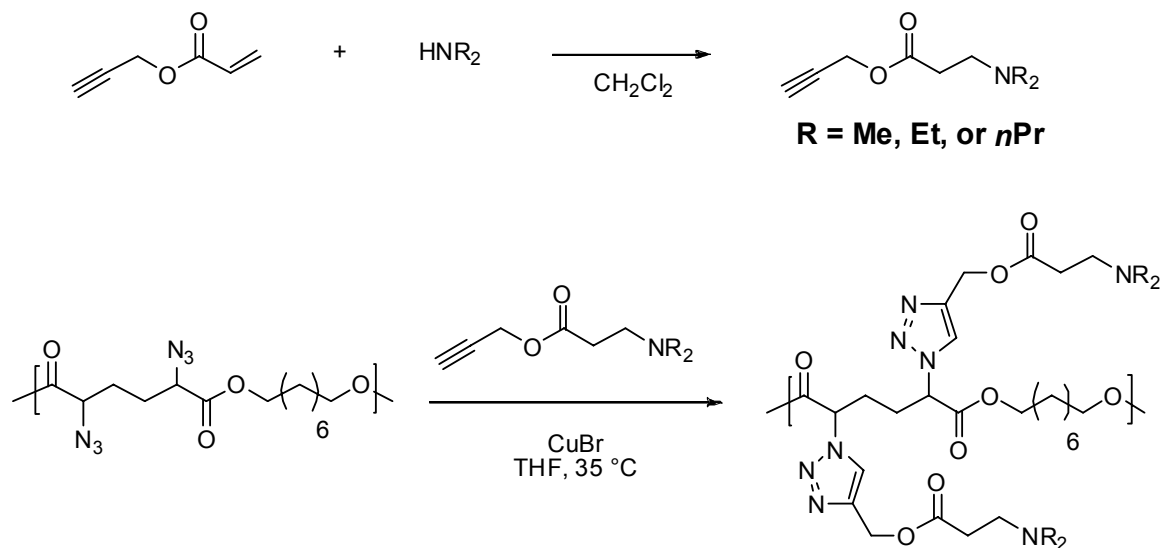
Figure 3.1. DSC thermograms of homopolymers and copolymers of N_3A :DEA:OD listed by mole fraction of N_3A repeat units in the polyester



Grafting of Amine-containing Alkynes. In order to form polymeric materials that would be able to condense, protect and deliver genetic material, amine-containing alkynes were reacted with the polyesters by copper-catalyzed azide-alkyne cycloaddition. A series of materials was designed to be a biodegradable analogue of a series of amine-functionalized poly(isoprene)s that was previously evaluated by our group as gene delivery vectors.³⁶ In the prior system, it was found that the size of alkyl side chain had a profound impact on toxicity, DNA binding and transfection efficiency. As the side group was changed from methyl to ethyl to propyl, both toxicity and DNA binding decreased. The diethylamino-functionalized polyisoprene was the best material evaluated in that study; it had lower toxicity and much higher transfection efficiency than PEI (~2 orders of magnitude) at an N/P ratio of 2. In the current work, we sought to characterize similar structure-property relationships in the polyesters, with the added benefit that the degradable structures would be less toxic. The click strategy also allows for each of the polycations to be derived from a common precursor, which minimizes molecular weight effects and allows for simpler optimization of the vectors. The parent polymer chosen for this study was poly(N₃A:OD) because it had the highest azide density and molecular weight. Previous studies have indicated that high molecular weight increases the transfection efficiency of synthetic vectors,³⁷⁻³⁹ so the largest parent macromolecule was desired.

In order to synthesize alkynes that contained the necessary tertiary amine groups, a series of Michael reactions was completed with the appropriate secondary amine and propargyl acrylate. Distillation of each reaction product gave pure compounds in good yields. These propargyl amines were then reacted with the poly(N₃A:OD) material under typical click conditions (Scheme 3.3). The final tertiary amine-containing polymers were isolated in high yields after the click reactions went to quantitative conversions as determined

by ^1H NMR (Table 3.4). Gel permeation chromatography analysis confirmed that the molecular weight of the resultant materials was high, although slight variations were observed (Figure 3.2). As the size of the alkyl side chain was increased, the apparent molecular weight of the polymer increased (relative to narrow polystyrene standards), which is expected as the hydrodynamic radius of the polymer increases. Each amine-containing polyester was amorphous and had a T_g that was approximately 20 $^\circ\text{C}$ higher than the precursor material. As the alkyl side chain, R, increased in size, the T_g decreased, indicating that longer alkyl chains can serve to plasticize the bulk material.



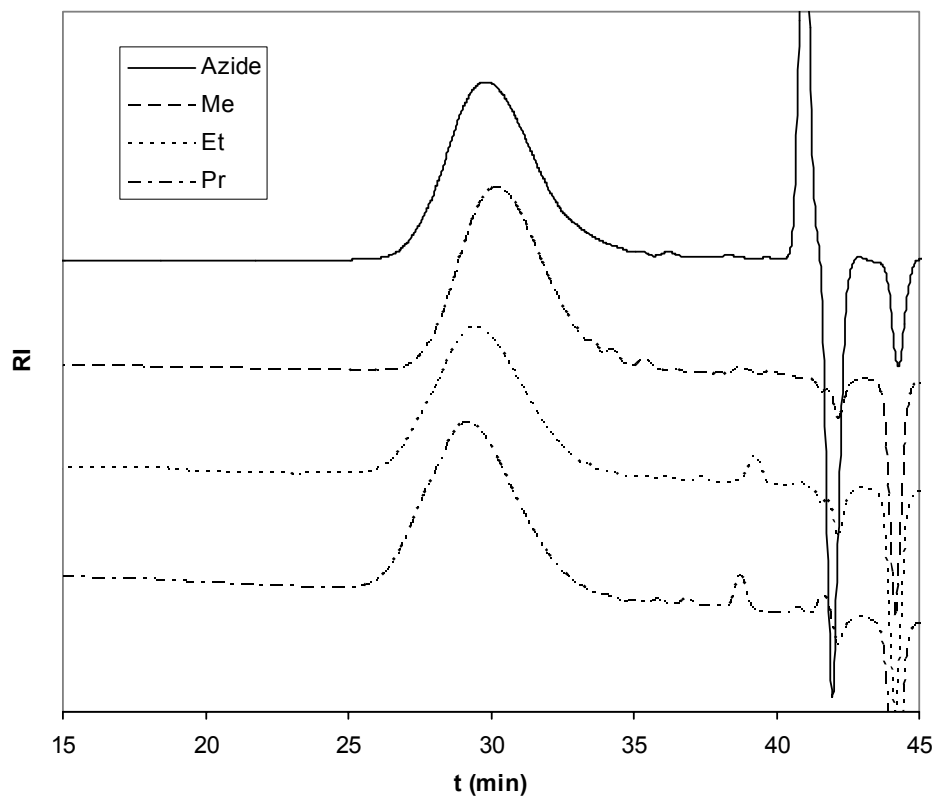
Scheme 3.3. Click reactions used to form alkyl amino polyesters

Table 3.4. Properties of amine-grafted polyesters derived from a common precursor, poly(N₃A:OD)

side group	$\langle M_n \rangle$ ($\times 10^{-3} \text{ g mol}^{-1}$) ^a	PDI ^a	T _g (°C) ^b	conversion (%) ^c	solubility pH 7.0 ^d	yield (%)
N ₃	11.2	1.7	-39	-	no	-
NMe ₂	9.5	1.6	-7	100	yes	86
NEt ₂	13.5	1.8	-10	100	yes	89
NnPr ₂	15.0	1.8	-18	100	yes	93

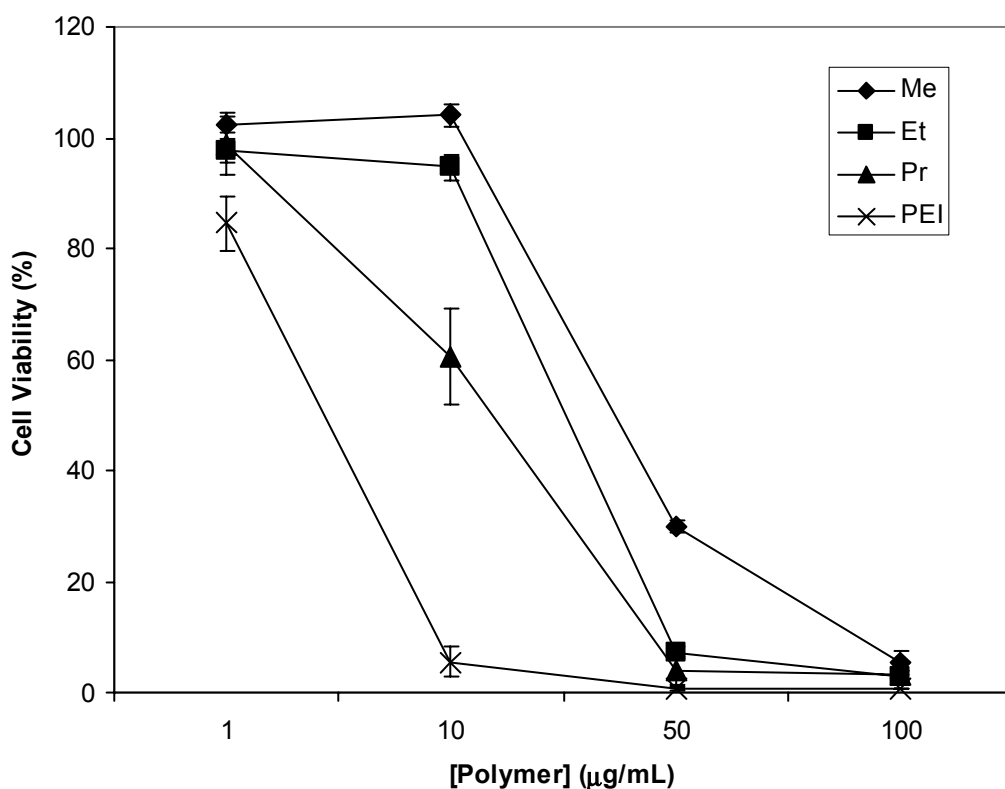
^a Determined by GPC in THF + 5 % NEt₃. ^b Determined by DSC, second heat, 10 °C min⁻¹. ^c Determined by ¹H NMR. ^d pH 7.0; 23 °C; 100 µg/mL.

Figure 3.2. Gel permeation chromatograms of parent azide polymer and alkyl amino polyesters



Titration. The series of polyesters was tested by titration to determine the pK_a of each. The polymers were protonated with hydrochloric acid, and the resulting solutions were titrated with 0.1 M sodium hydroxide solution. It was found that the pK_a of the polycations depended on the alkyl group. The dimethylamino polyester buffered over a range centered at pH 7.8; ethyl did so at pH 7.6; and propyl had a pK_a of 6.5. Thus, as the length of the alkyl group increased, the acidity increased.

Figure 3.3. Relative toxicity of alkylamino polyesters and PEI control as determined by the MTS assay



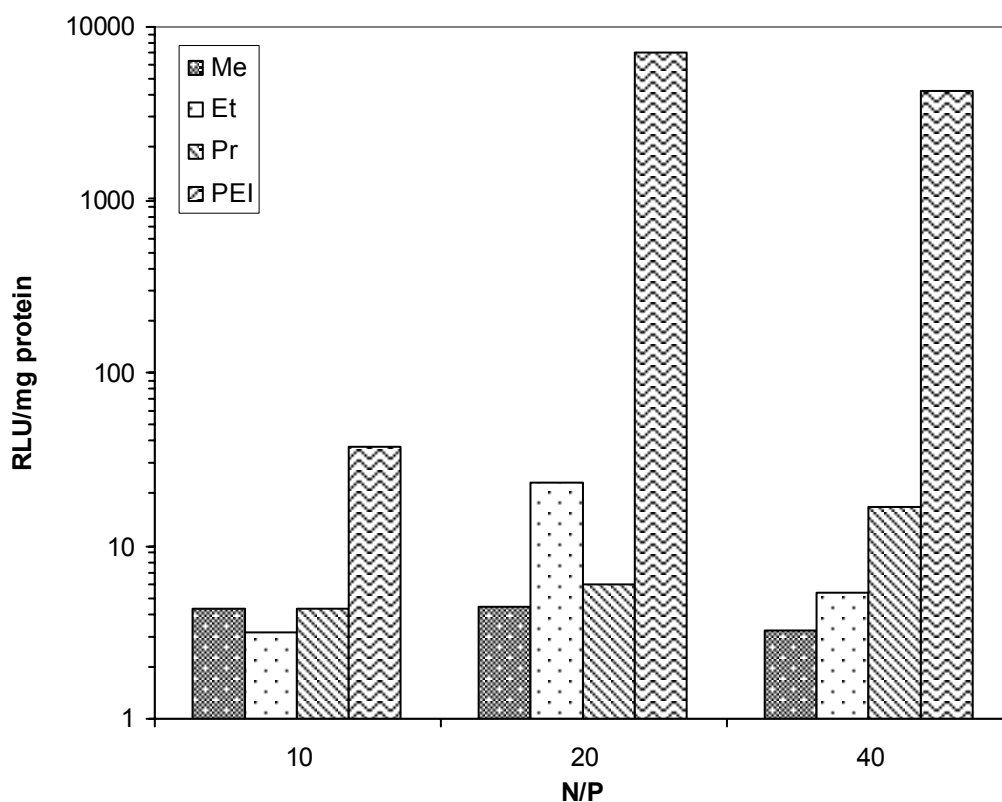
Toxicity. The toxicity of the polyesters was evaluated by exposing concentrated solutions to HeLa cells. After incubation in the presence of the polymer at concentrations from 1 – 100 μg/mL, the viability of the cells was quantified using the MTS assay. The

polymers were compared to branched PEI with a similar molecular weight ($\langle M_n \rangle$ 1×10^4 g/mol; PDI 2.5) as a control. The results of this assay are shown in Figure 3.3, and they demonstrate that the degradable materials are less toxic than PEI, and that toxicity increases (Pr > Et > Me) as the acidity of the polyplex increases. These materials are slightly less toxic than the nondegradable amine-functionalized polyisoprene materials that were previously studied,³⁶ although direct comparisons are difficult since the amine density of each series differs greatly.

Gene Transfection. Given the favorable toxicity results of the alkyl amino polyesters, each was evaluated for its gene transfection efficiency. The polymers were allowed to associate with plasmid DNA, and then the polyplexes were exposed to HeLa cells at N:P ratios of 10, 20, and 40. Transfection efficiency was measured by the luciferase assay, and the results of the experiment are shown in Figure 3.4. In these studies, PEI was much more effective at transfection than the polyester materials. These preliminary experiments indicated that the amine-containing polyesters have insufficient properties required for gene transfection, likely due to insufficient buffering properties. Efficient vectors must contain protonated amines at pH 7.4 to condense DNA, and those polyplexes must bear a net positive charge to promote cell binding and endocytosis. Once inside the endosome, the polyplex must be able to destabilize the endosomal matrix to release the cargo into the cytoplasm. This is often accomplished by the protonation of remaining neutral amines, resulting in endosomal rupture due to an osmotic imbalance (proton sponge effect).⁴⁰ In order to accomplish this, a polymer must have a strong buffering capacity with a pK_a near physiological pH. When the alkyl group is methyl or ethyl, the materials may be too basic to promote endosomal rupture by the proton sponge effect, because there are likely not enough neutral amines to induce the proton sponge effect. The dipropylamino-functionalized

polyester may be too acidic to form stable polyplexes and encourage endocytosis at pH 7.4 because it does not bear a net positive charge. The click reaction, however, will allow the pK_a of new polyplexes to be tuned and the buffering capacity to be enhanced by choosing the appropriate ratio of amino alkynes. In this system, a copolyester with both dipropylamino and diethylamino side chains should result in a polymer that can buffer in the optimal pH range.

Figure 3.4. Transfection efficiency of HeLa cells with pCMV-Luc of alkyl amino polyesters and PEI control



3.4 Conclusions

A new monomer, diethyl 2,5-diazidoadipate, was synthesized and polymerized into amorphous, high molecular weight polyesters and poly(ester-ethers) by an enzyme-catalyzed transesterification. Copolymerizations with diethyl adipate yielded random copolymers with the desired ratio of repeat units and various thermal properties. The azide groups were quantitatively converted to substituted 1,2,3-triazoles by reacting with terminal alkynes via Cu(I)-catalyzed cycloadditions. Amine-containing alkynes were synthesized and grafted onto a common polyester precursor to produce novel gene transfection vectors. The polymers were less toxic and less efficient in gene transfection assays than branched PEI. Further characterization of the polymer and polyplex properties will allow rapid iterative optimization of the gene transfection vectors by the design and synthesis of new functional polymers by click chemistry.

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Chapter 4

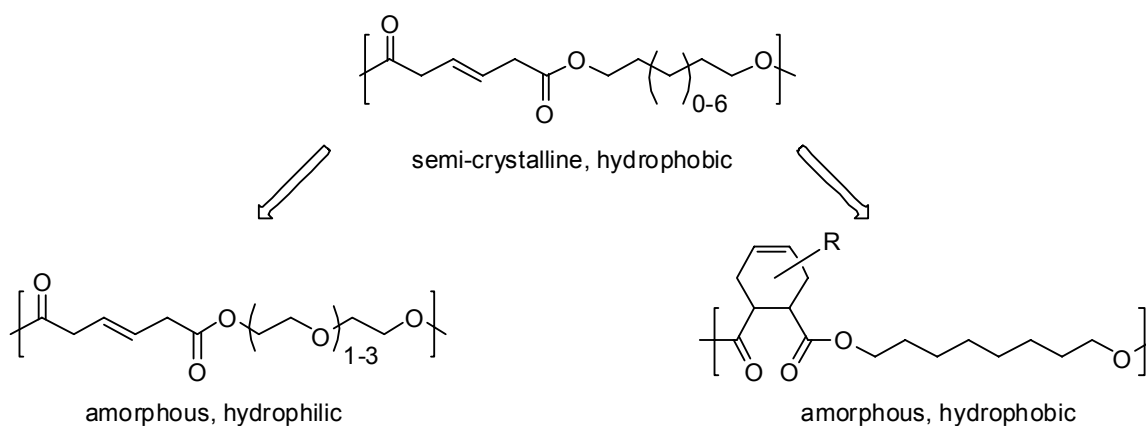
HYDROLYTIC DEGRADATION OF AMORPHOUS ELASTOMERS DERIVED FROM HYDROPHOBIC DIELS-ALDER POLYESTERS

4.1 Introduction

Previous reports from our group described the synthesis and characterization of amorphous polyesters and elastomers based on trans- β -hydromuconic acid (HMA).^{1, 2} The polymerization of HMA with oligo(ethylene glycol)s yielded unsaturated, amorphous, liquid polyesters that could be cured in radical crosslinking reactions to yield amorphous elastomers with mechanical properties similar to elastin-rich soft tissues. The use of oligo(ethylene glycol)s ensured that the materials would be amorphous and hydrophilic. Maintaining amorphous character in these materials allowed for soft, flexible elastomers to be easily synthesized. The hydrophilic character of the diols resulted in elastomers that completely degraded *in vitro* in as little as 35 days. The speed of the degradation was due to the high diffusivity of water and degradation byproducts through the hydrophilic matrix, which facilitated hydrolytic cleavage of the ester bonds. The degradation profiles of each of these materials were linear with respect to time, which is expected to be beneficial in predicting loss of mechanical properties or release of a drug from the degrading matrix over time.³⁻⁵

In order to slow elastomer degradation, it is necessary to decrease the diffusivity of water and degradation byproducts through the elastomer matrix. In order to do this, matrix permeability and/or water solubility must be decreased. Decreasing the permeability of the material can be accomplished by synthesizing a semi-crystalline material or by increasing the crosslink density. Synthesis of a semi-crystalline elastomer would greatly reduce the ease of processing the pre-polymer and result in undesired multistep degradation processes.⁶ Therefore, a method was sought to increase the crosslink density and reduce the water solubility of the polyester, while maintaining the amorphous character.

Inspection of the structure-property relationships in the HMA systems reveals that changing from an alkyl diol to an ether-containing diol simultaneously alters the solubility and thermal properties of the material, as shown in Scheme 4.1. In order to implement the above strategy, the alkyl diol was retained, but the diacid component was changed to a hydrophobic, bulky group. The dicarboxylate monomers were formed using Diels-Alder (D-A) reactions, and each proved bulky enough to disrupt crystallization, but not so large that the glass transition temperatures of the material were greatly increased.⁷ Also, the D-A repeat units contained crosslinkable groups, which were required for elastomer formation.



Scheme 4.1. Comparison of structure-property relationships in unsaturated HMA-based polyesters and Diels-Alder polyesters

A series of elastomers was successfully synthesized from these polyesters, and they were found to have comparable mechanical properties to the HMA-based materials and soft tissues. This report details the degradation of the D-A elastomers and the relationship between the degradation rates, elastomer crosslinking density and hydrophobicity.

4.2 Experimental Section

Polymer and Elastomer Synthesis. Previously published synthetic procedures were used for the polymers and elastomers.⁶

Mechanical Analysis. Mechanical data were collected on an Instron 5566 at a crosshead speed of 10 mm/min (approximately 100 % extension per min) at 25 °C. The Young's modulus (E) was calculated using the initial linear portion of the stress/strain curve (0 – 5 % strain). The crosslinking density ν was calculated according to the following equation:

$$\nu = \frac{E}{3RT}$$

where R represents the universal gas constant and T is the temperature in K. Each measurement was performed on three separate samples. The value was reported as the average of the three measurements.

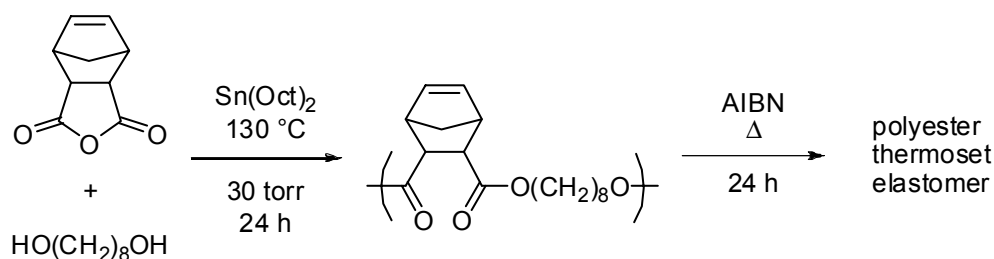
In Vitro Degradation. Elastomer films (0.10 g) were placed in 20 mL of 0.01 M pH 7.4 phosphate buffered saline solutions at 37 °C. The films were removed from the buffer solution at weekly intervals, rinsed with deionized water, and dried under vacuum for 24 h before their mass was measured. Each measurement was performed on three separate samples. Error bars represent a 95 % confidence interval. Mass percent remaining (MR) was calculated according to the following equation:

$$MR = \left(\frac{m_i - m_t}{m_i} \right) \times 100$$

where m_i and m_t represent the initial mass and mass at time t. Average MR was plotted against time, and the data was analyzed according to zero-order kinetics.

4.3 Results and Discussion

As previously reported, the Diels-Alder reaction was used to synthesize a family of dicarboxylate monomers that could be condensed with alkyl diols to form high molecular weight polyesters. By allowing maleic anhydride to react with dicyclopentadiene, a norbornene-based anhydride was synthesized, which was polymerized in a step growth reaction with a slight excess of 1,8-octanediol in the presence of tin(II) 2-ethylhexanoate catalyst (Scheme 4.2). The reactions proceeded at 130 °C under vacuum to yield amorphous liquid polyesters ($\langle M_n \rangle = 3.0 - 5.0 \times 10^3 \text{ g mol}^{-1}$; $T_g = -40$ to -30 °C).



Scheme 4.2. Synthetic strategy for preparing unsaturated aliphatic polyesters and elastomers

To exploit the unsaturation in each repeat unit to synthesize elastomers, each polyester was mixed with 5 wt. % AIBN and cured at high temperatures for 24 h (Scheme 4.2). The resulting materials showed a broad range of mechanical properties, as shown in Table 4.1. Instron analysis allowed for the determination of the Young's modulus (E) of each material, which in turn was used to calculate the crosslinking density (ν). The elastomer cured at $130\text{ }^\circ\text{C}$ had the lowest crosslink density, with 7.0 mmol/L , while increasing T_{cure} to $145\text{ }^\circ\text{C}$ allowed for a crosslink density of 60.4 mmol/L . A drastic increase in crosslink density ($\nu = 1560\text{ mmol/L}$) was observed in the materials crosslinked at $160\text{ }^\circ\text{C}$.

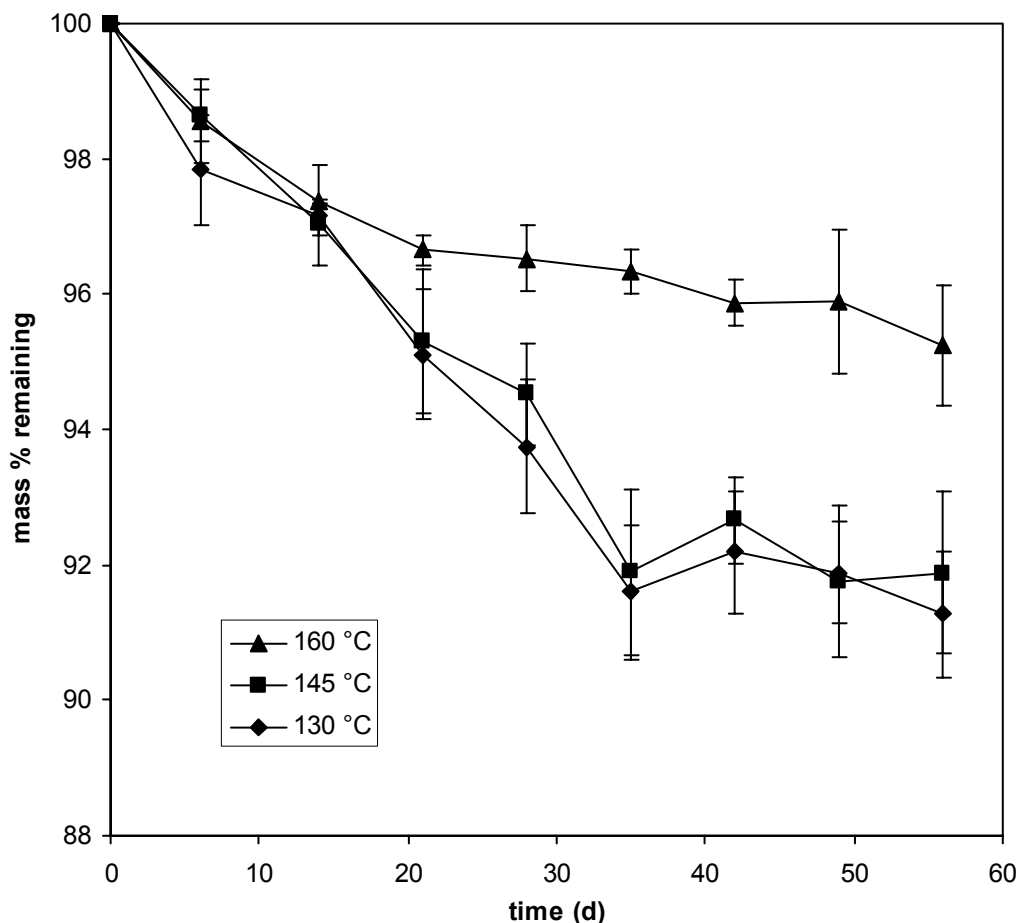
Table 4.1. Properties of elastomers formed by thermal crosslinking for 24 h using 5 wt % AIBN at the given temperature

elastomer	T _{cure} (°C)	T _g ^a (°C)	E ^b (MPa)	σ ^b (MPa)	ε ^b (%)	ν ^b (mmol/L)	k _{mass} ^c (% mass loss d ⁻¹)
D-A1	130	-16	0.05	0.08	195	7.0	0.16
D-A2	145	-12	0.4	0.4	161	60.4	0.15
D-A3	160	-15	11.5	1.5	87	1560	0.07

^a Determined by DSC, second heat, 10 °C/min. ^b Determined by Instron, 10 mm/min crosshead speed. ^c Zero-order rate is the negative of the slope of MR versus *t*.

The degradation of the elastomers was studied *in vitro* for eight weeks to investigate the extent to which the crosslink density and hydrophobicity of the materials would impact the kinetics of hydrolysis. The degradation profiles of the amorphous materials were linear as expected (Figure 4.1). The materials degraded very slowly; each elastomer maintained greater than 90 % of its original mass after eight weeks. It was observed that the rate of degradation exhibited an inverse linear dependence on crosslinking density. This is due to the decreased permeability of the matrix, which prevents diffusion of water and degradation byproducts through the thermoset. Over the course of this time period, two of the elastomers (T_{cure} = 130 or 145 °C) degraded at rates that were not statistically different at a 5 % confidence interval.

Figure 4.1. Mass loss of elastomers cured at different temperatures



The D-A elastomers degraded about an order of magnitude more slowly than the hydrophilic HMA-based materials. The D-A elastomers degraded at a rate of 0.07 – 0.16 mass percent per day, while the HMA materials cured under similar conditions (130 °C for 24h with 5.0 wt % of BPO) degraded with a rate of 1.1 – 2.8 mass percent per day.² The hydrophobic D-A matrices decrease the diffusivity of water and degradation byproducts through the devices, decreasing the rate of hydrolysis. The D-A materials provide a means of controlling the thermal properties of aliphatic polyesters independent of the solubility properties, allowing the production of amorphous elastomers that degrade slowly.

4.4 Conclusions

The thermal crosslinking of Diels-Alder derived polyesters allowed for the formation of degradable elastomers. The rate of the linear degradation depended on the crosslinking density of the matrix and was found to be much slower than those found for hydrophilic counterparts.

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4.5 References

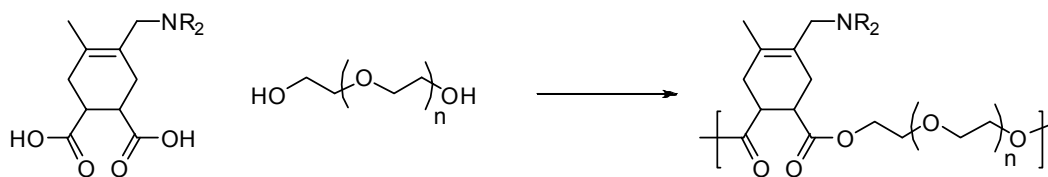
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Chapter 5

GENERAL CONCLUSIONS

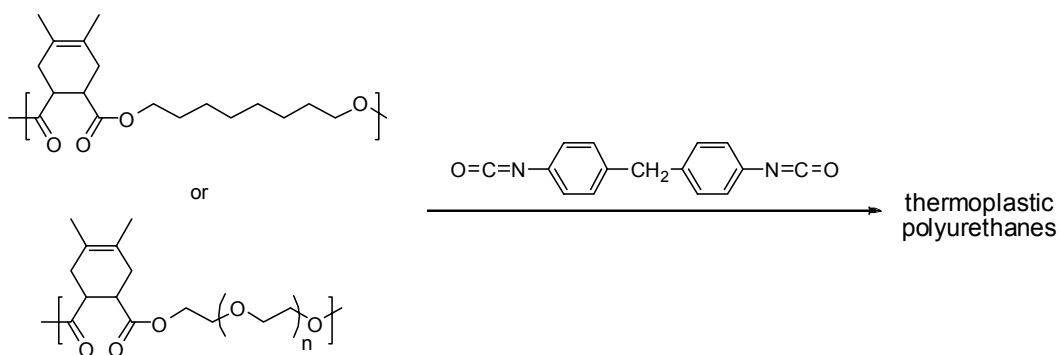
While the synthesis of new aliphatic polyesters has undergone a shift towards more diverse functionalization methodologies, ring-opening polymerizations have been employed in a large majority of the research. The unique advantages to step-growth polymerization are demonstrated here by the wide range of materials derived from a relatively small set of parent monomers. The [4+2] and [3+2] cycloaddition reactions have allowed for the inclusion of polar and reactive groups into aliphatic polyesters, namely tertiary amines, ethers, and azides. As the field advances, more diverse and creative methodologies will be required to produce materials with the desired functional groups, thermal properties, solubility, polymer architecture, and degradation properties. The chapters presented in this dissertation described the creation of new synthetic methodologies based on a combination of cycloaddition reactions and step-growth polyesterification that produced materials with novel polymer properties.

Chapter 2 described the synthesis of a new class of dicarboxylic acid and anhydride monomers that resulted in amorphous polyesters with low glass transition temperatures. Depending on the diene that was used in the Diels-Alder reaction, materials with a variety of alkene reactivity and polar functionality were obtained. Amine-containing copolyesters were synthesized successfully containing up to 50 % of the amine repeat unit, and further studies in our group have increased the amine content and water solubility of these types of polymers. These materials are currently being studied as degradable gene transfection vectors. The step-growth polymerization method allows for optimization of the polymer backbone by the choice of different diols, while the Diels-Alder reaction allows for independent optimization of the amine structure by the choice of different dienes. (Scheme 5.1)



Scheme 5.1. Synthesis of amine-containing polyesters based on the Diels-Alder methodology described in Chapter 2

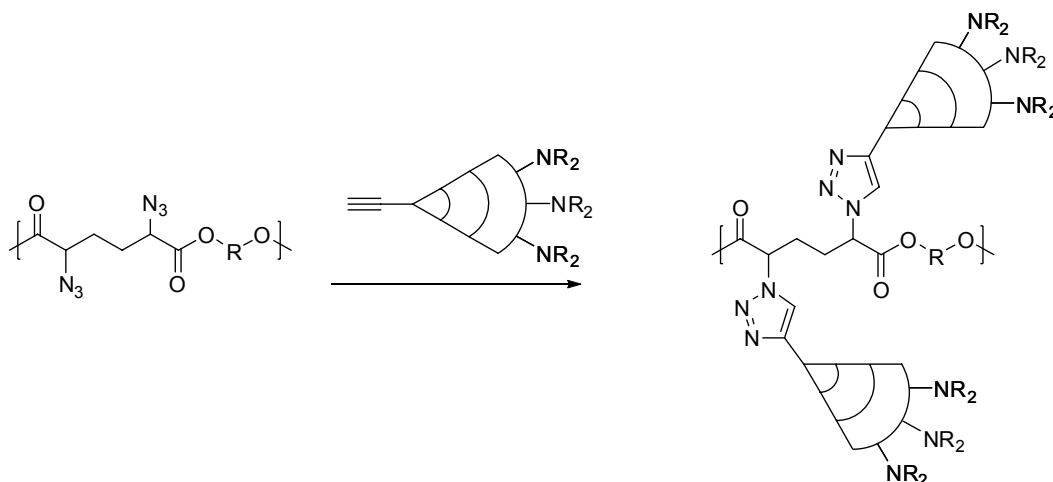
Norbornene-based prepolymers were used for the synthesis of amorphous, nontoxic elastomers. The degradation of these elastomers is described in Chapter 4. Similar prepolymers were also used to prepare thermoplastic polyurethanes by reaction with diisocyanates.¹ These materials, depicted in Scheme 5.2, exhibited excellent mechanical properties, were degradable, and were nontoxic. This small set of precursors has generated structures with a broad range of mechanical properties and permitted the production of new degradable thermoset or thermoplastic elastomers for a wide variety of biomedical applications.



Scheme 5.2. The use of the norbornene-based prepolymers to produce thermoplastic polyurethanes

Cycloaddition reactions were also explored to modify step-growth polyesters in mild post-polymerization reactions. Using the highly selective azide-alkyne dipolar cycloaddition,

amine-containing side groups were grafted onto polyesters. These materials were tested for toxicity and gene transfection efficiency. While the materials were nontoxic, the transfection efficiency was low relative to a branched PEI control. Fortunately, the versatility of the click strategy will allow rapid iterative optimization of DNA delivery vectors. Initially, the charge and buffering capacity of the material must be controlled; this can be approached by synthesizing novel amino-alkynes that can be clicked onto the polyester backbone. The production of dendri-graft polymers² will likely be an important method of increasing the amine density and buffering capacity of the polyester (Scheme 5.3).



Scheme 5.3. Proposed structure of dendri-graft polyesters with increased amine density, where the wedges represent dendrons arrayed with amine groups

The grafting reaction is mild and also allows for a variety of functionalized alkynes to add utility to the vectors.³ For example, poly(ethylene glycol) grafts can prevent polyplex aggregation and increase circulation times. More sophisticated bioconjugation techniques are also possible; moieties like folate, integrins, and transferrin can actively target specific cell types and enhance endocytosis by invoking receptor-mediated pathways. Fusogenic

peptides have also been shown to aid in the release of vectors and their cargo from endosomes.⁴ The incorporation of these types of groups will lead to “smart” delivery vehicles that are tailored to specific therapeutic objectives.

Step-growth polymerizations and cycloaddition reactions have been employed in the search for new functional aliphatic polyesters for biomedical devices. The unique combination of these two strategies has produced a new synthetic space for the study and optimization of degradable materials.

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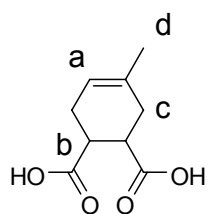
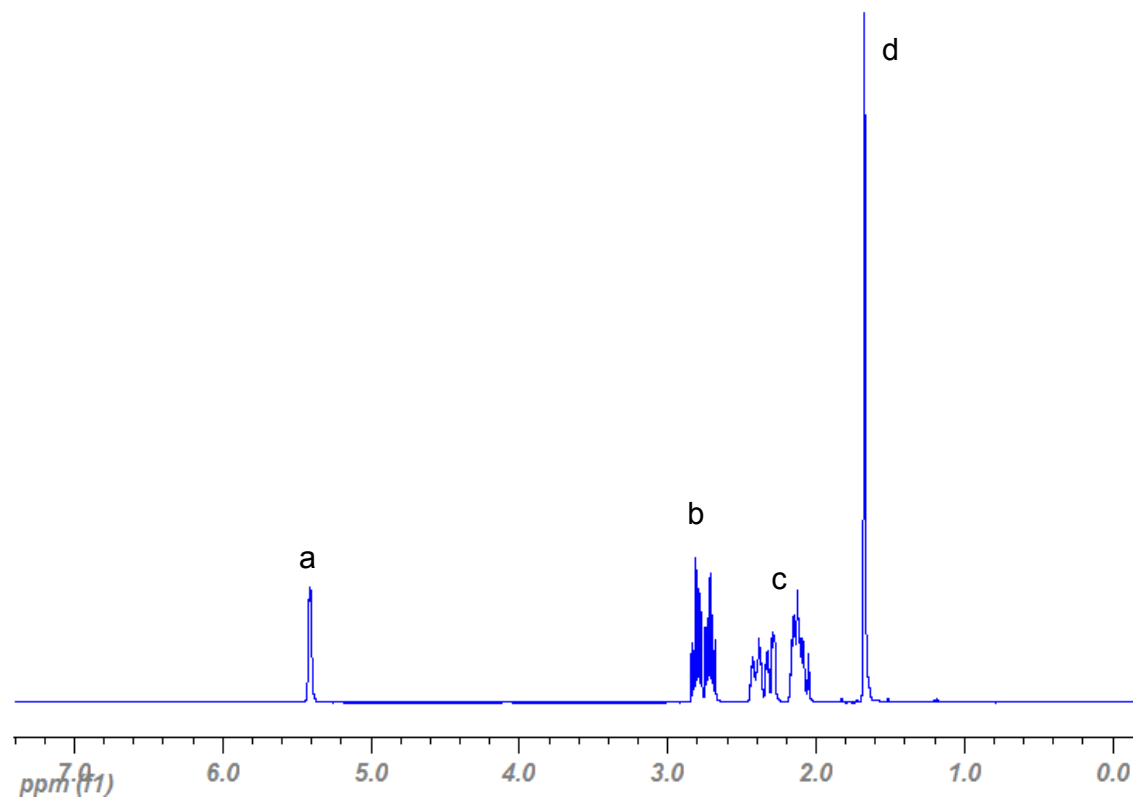
Appendix A

SUPPLEMENTAL MATERIALS FOR CHAPTER 2

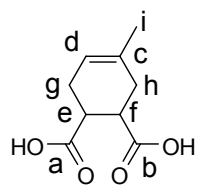
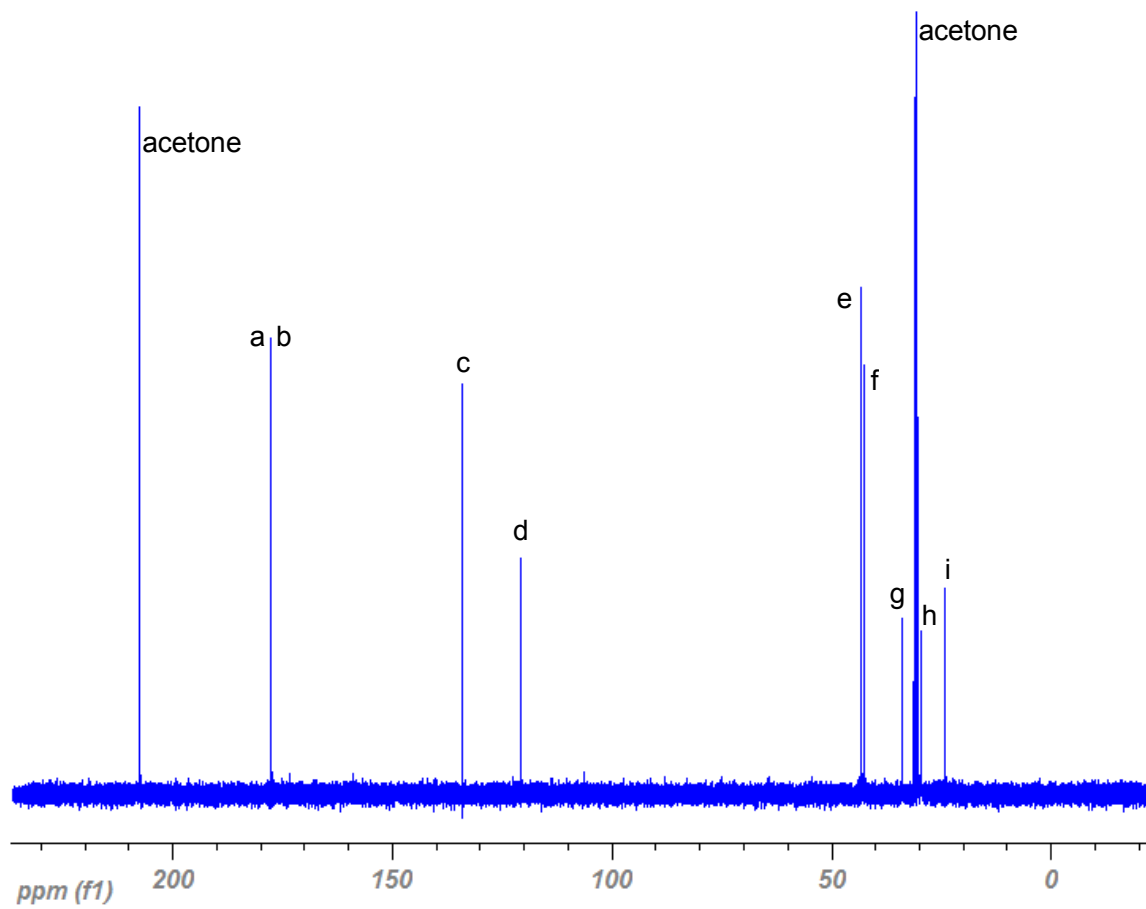
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Representative ^1H NMR and ^{13}C NMR Spectra with Assignments

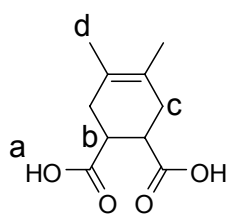
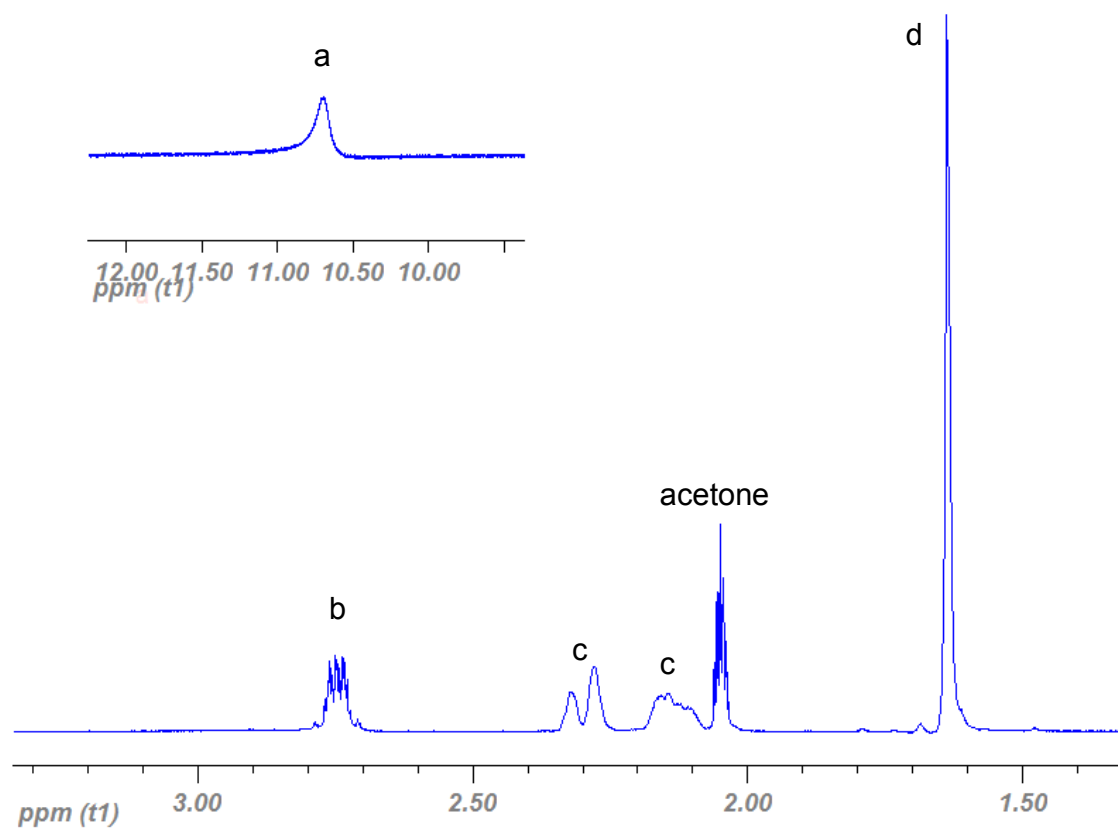
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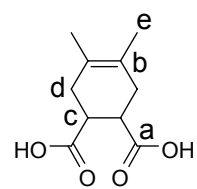
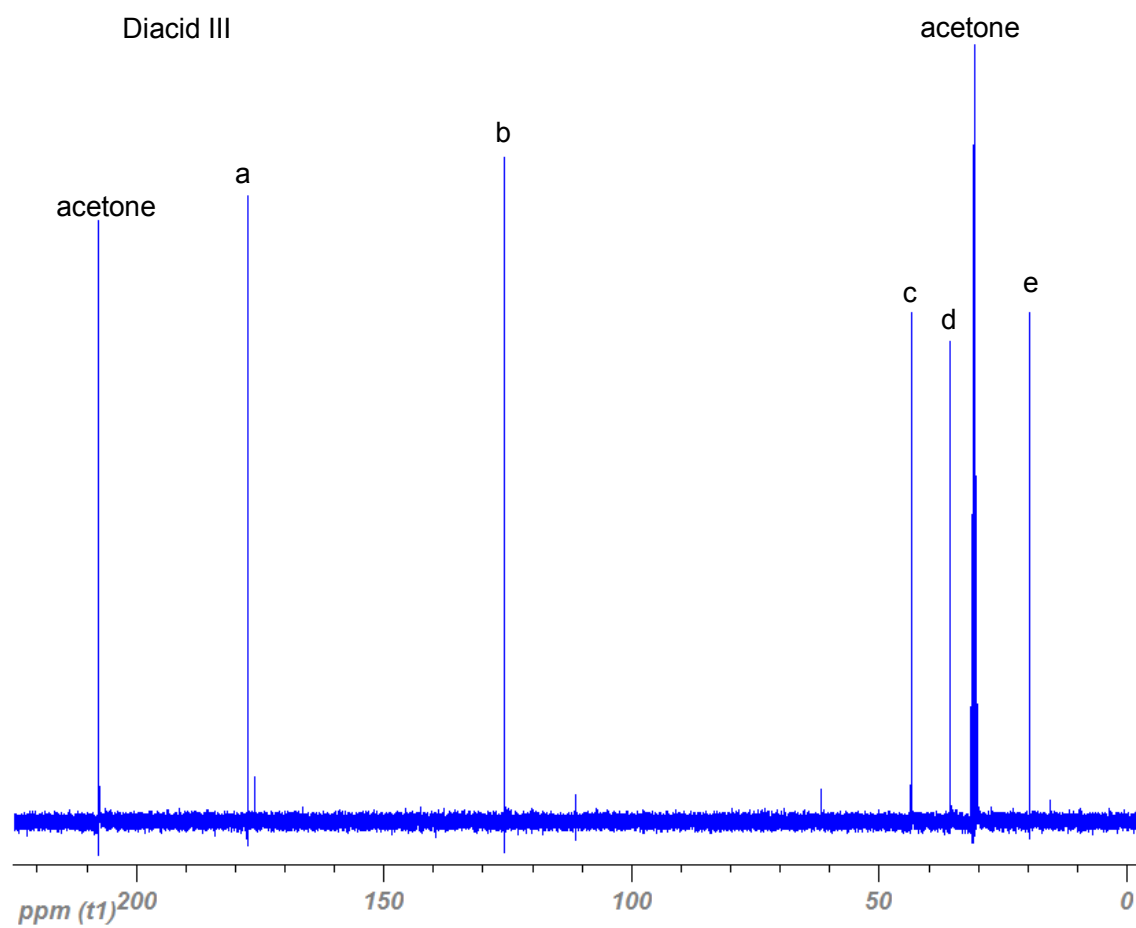


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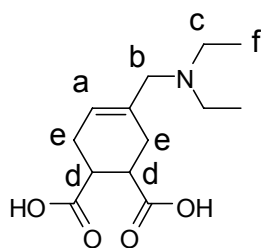
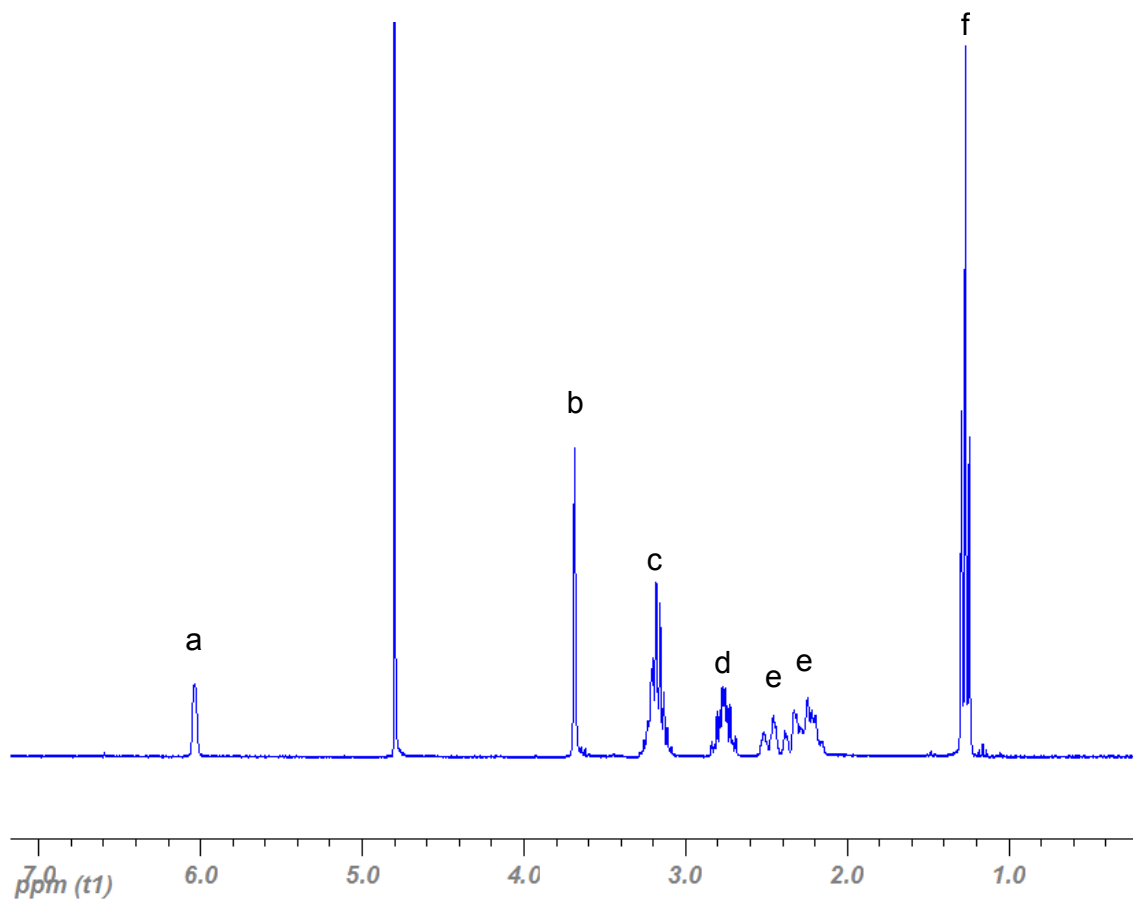


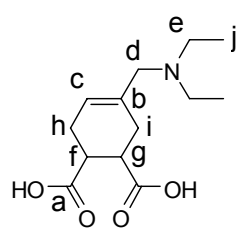
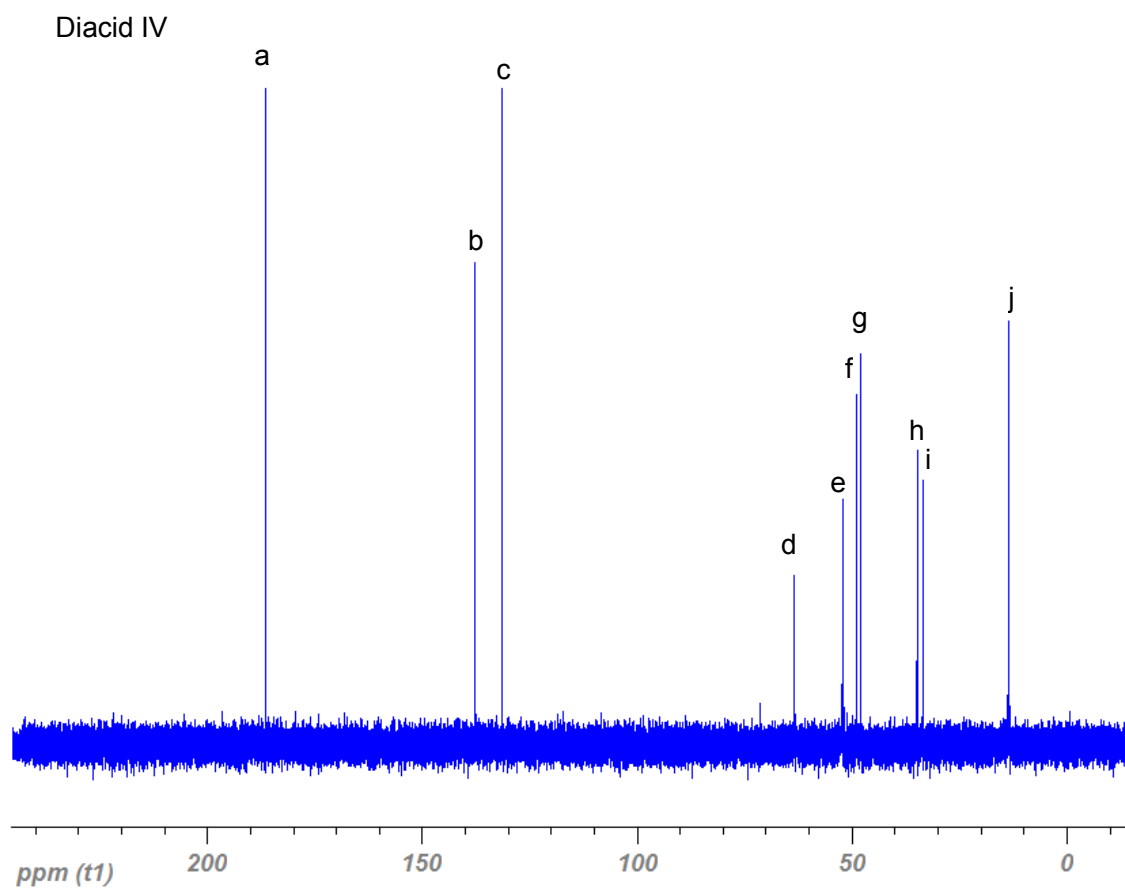
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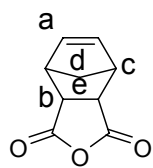
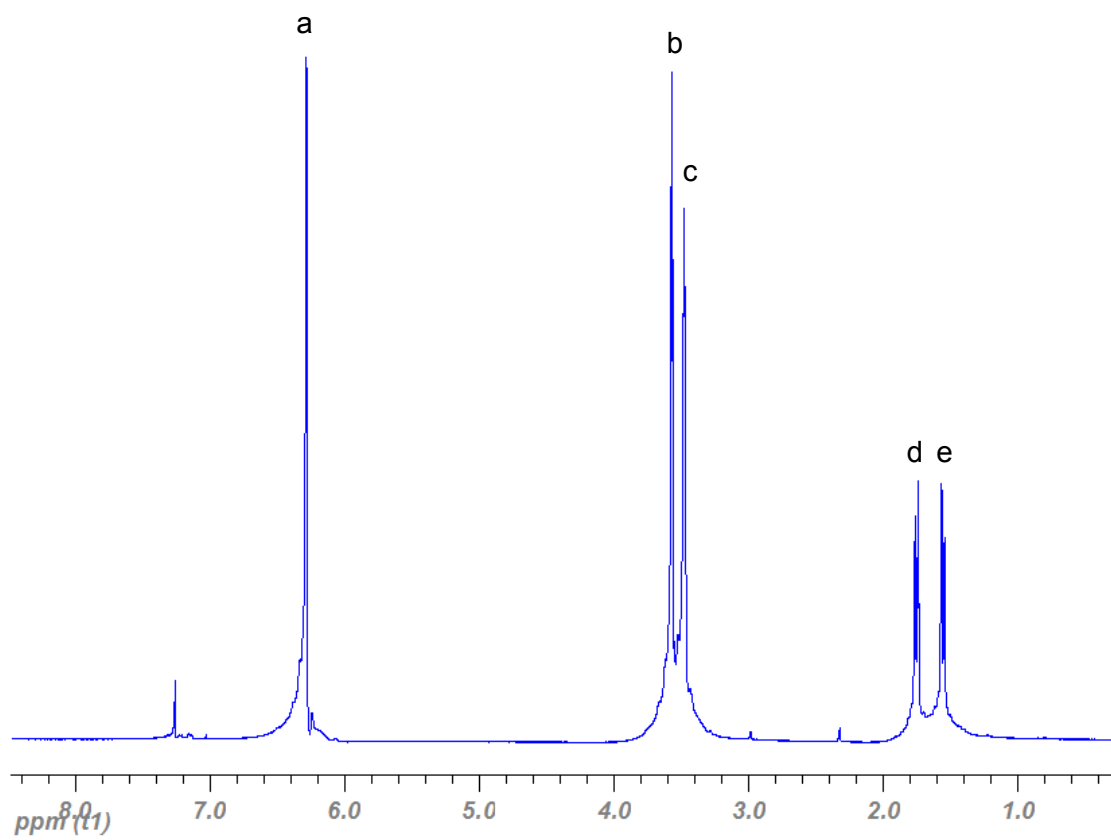


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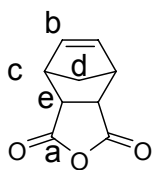
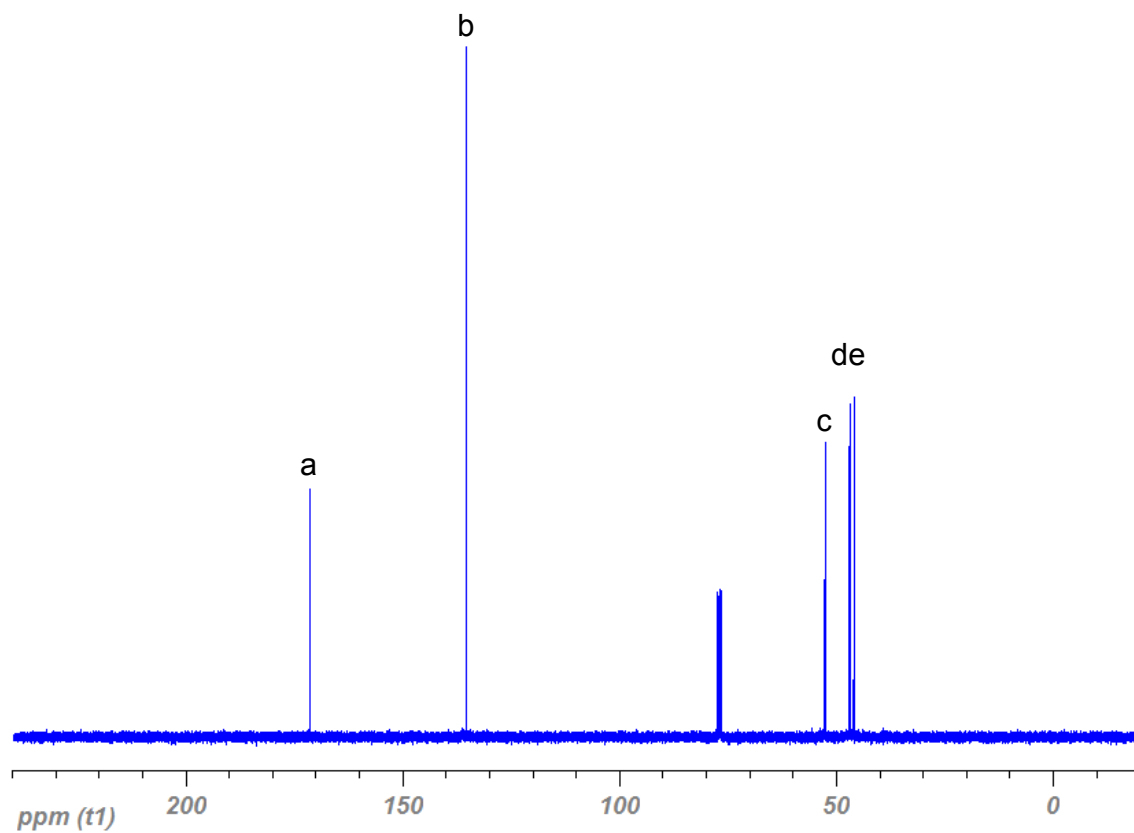




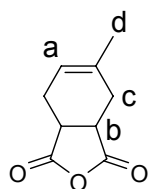
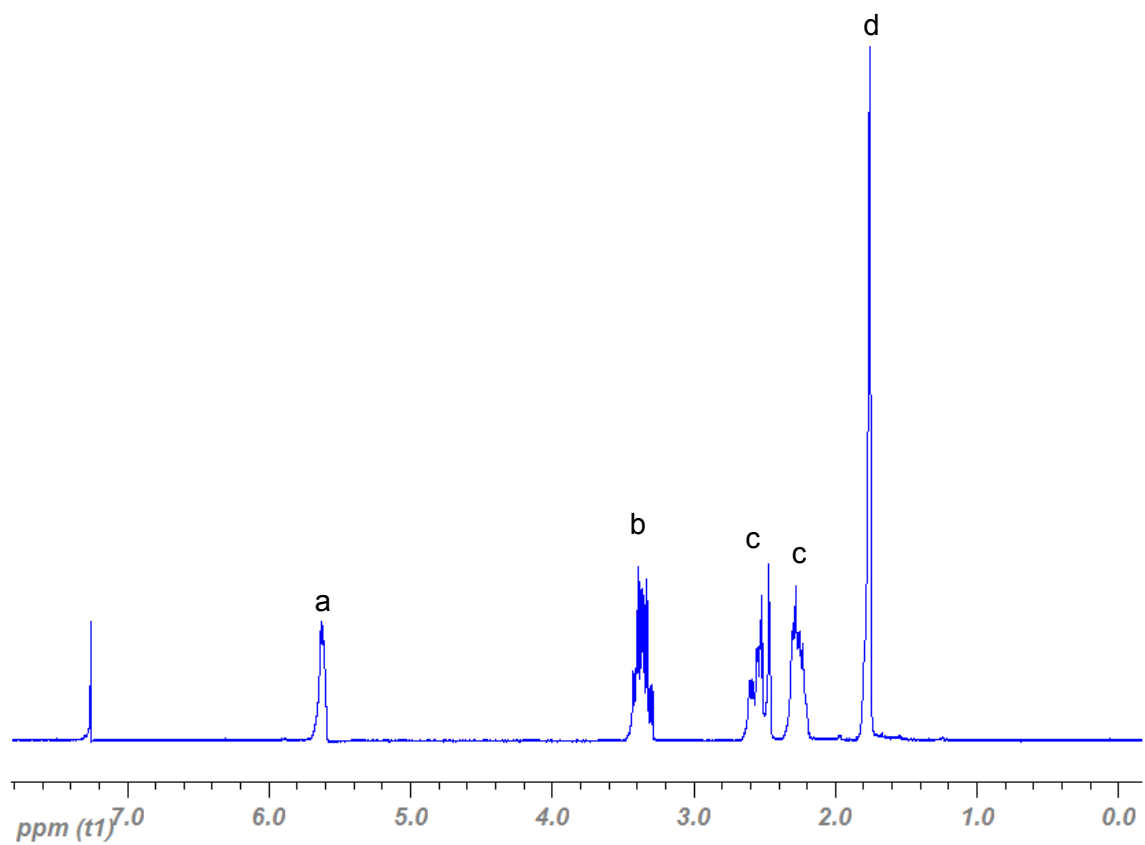
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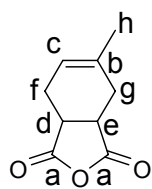
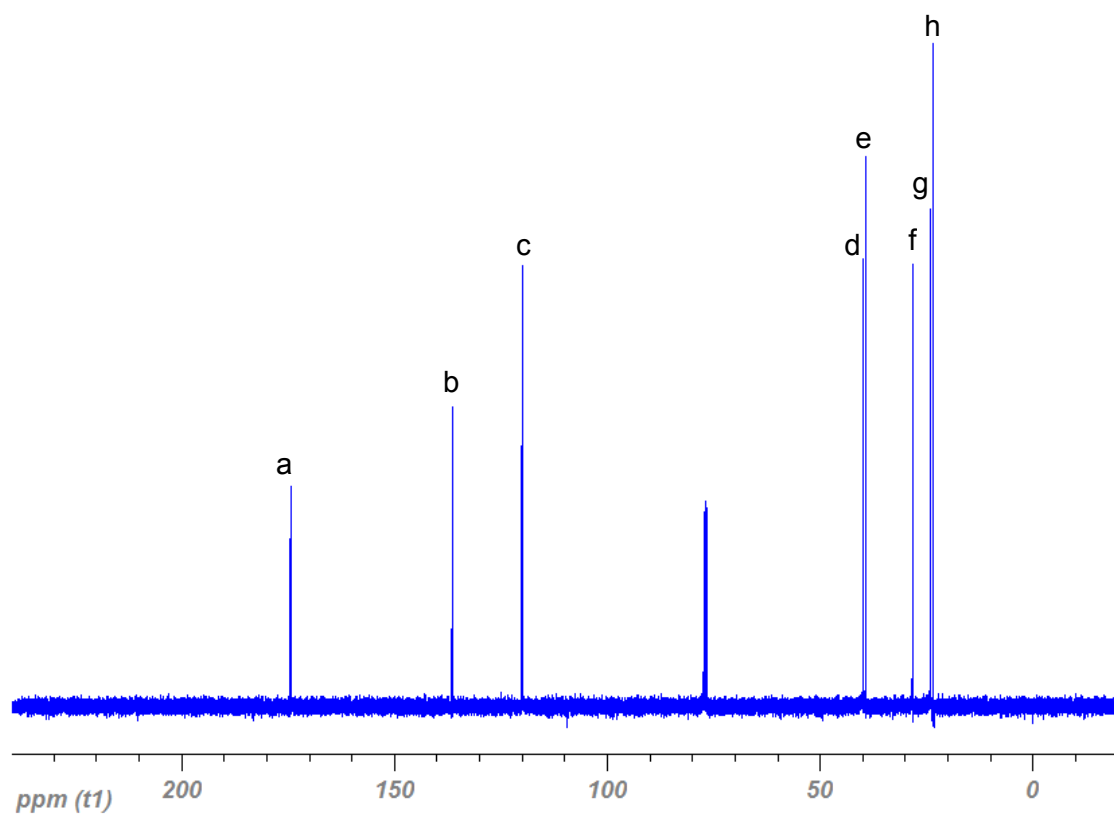
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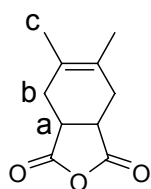
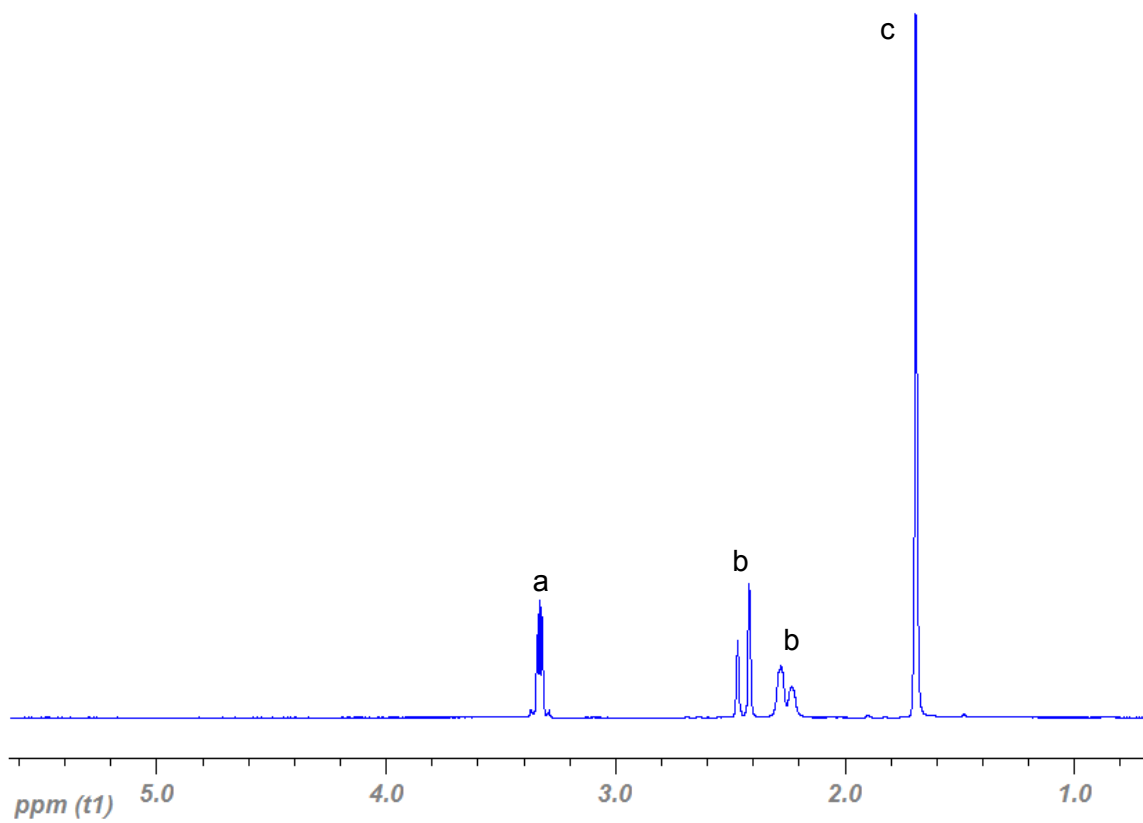
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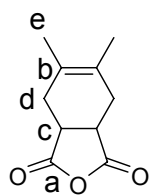
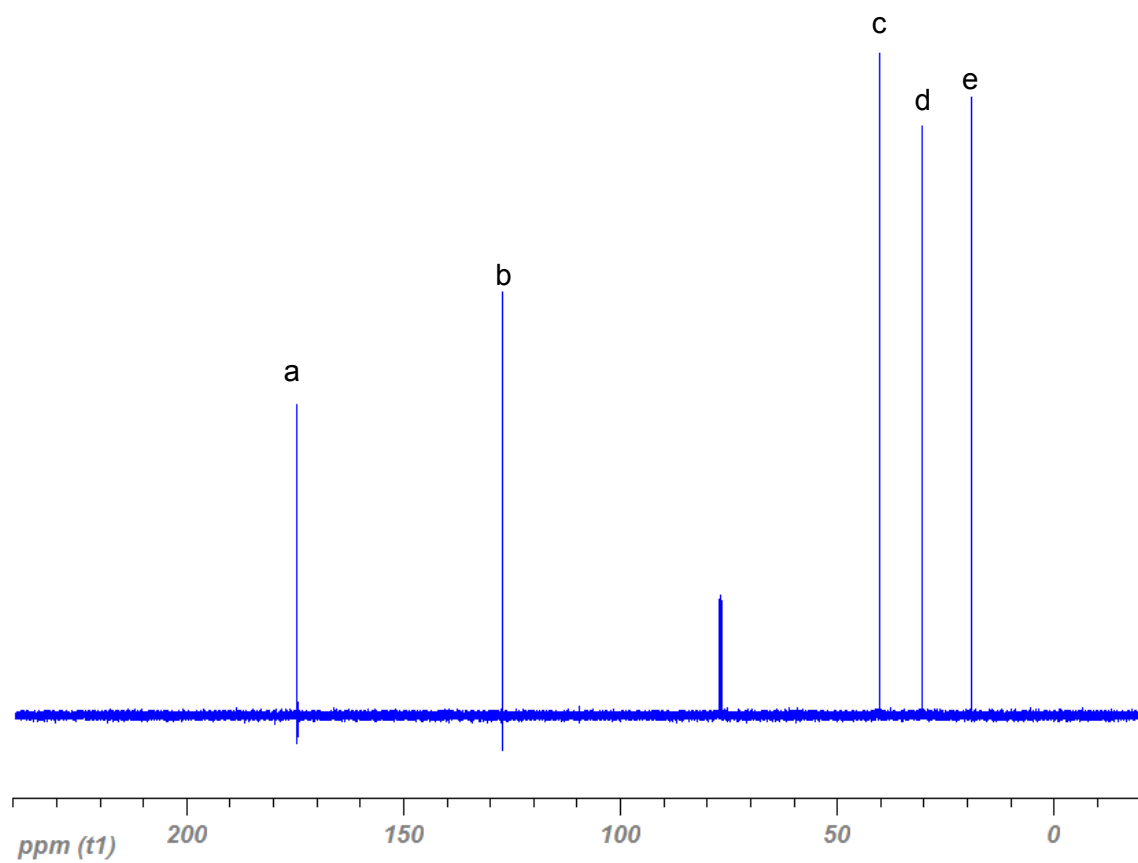
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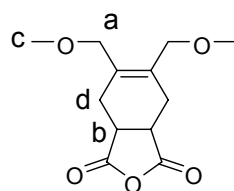
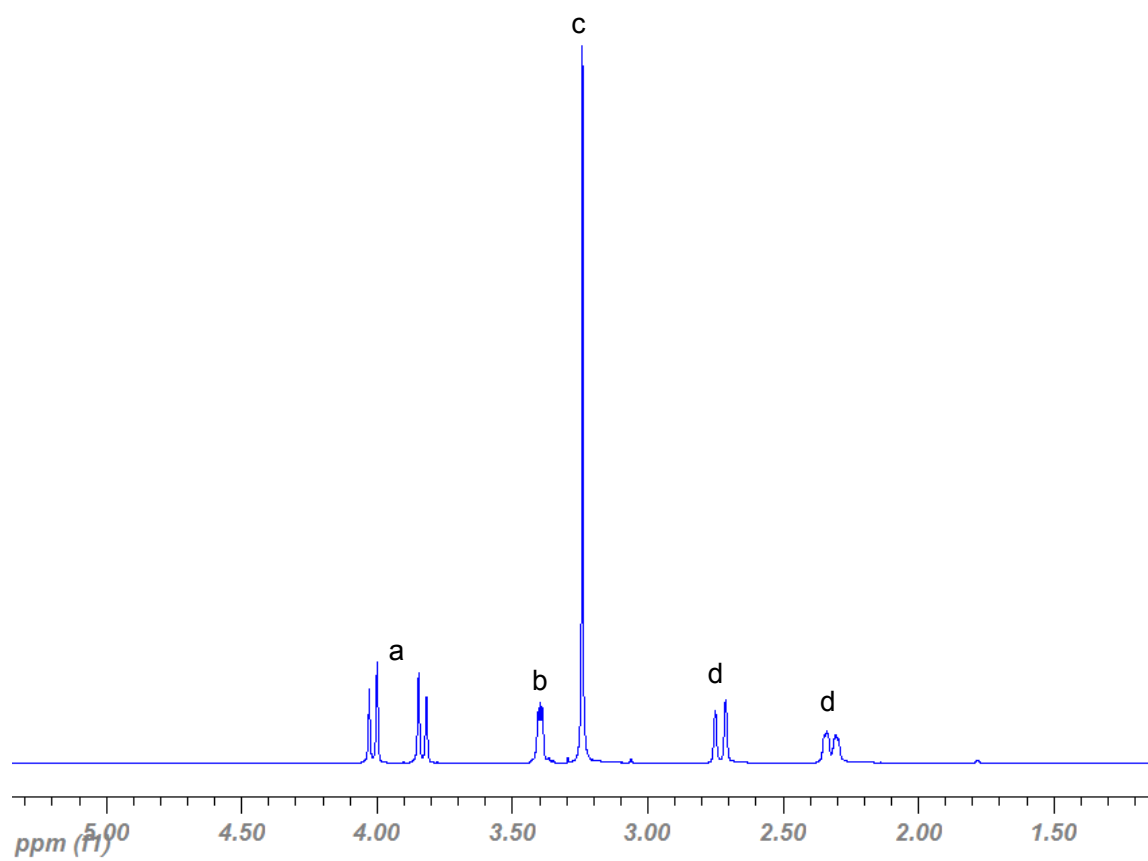
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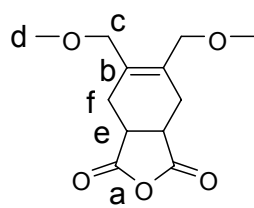
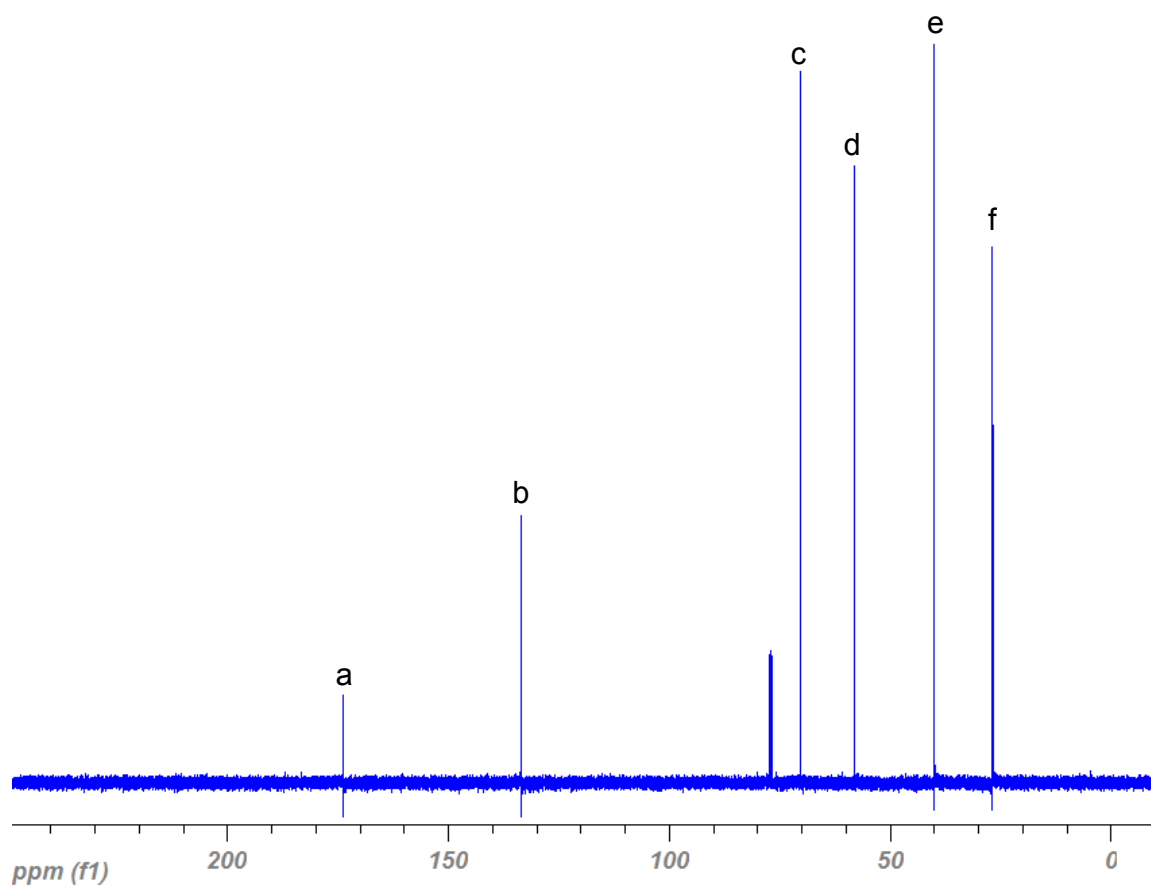
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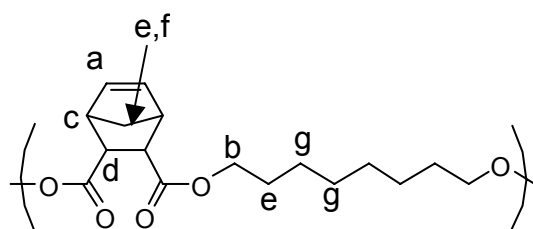
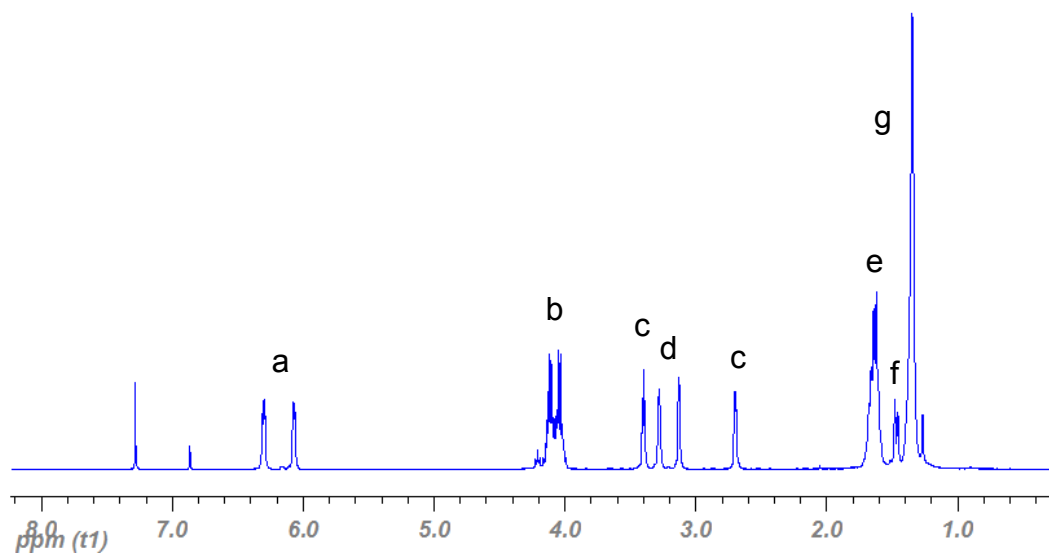
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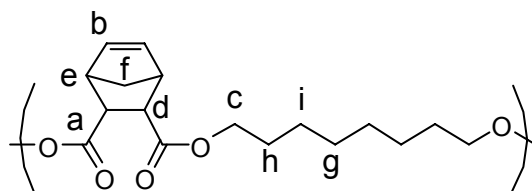
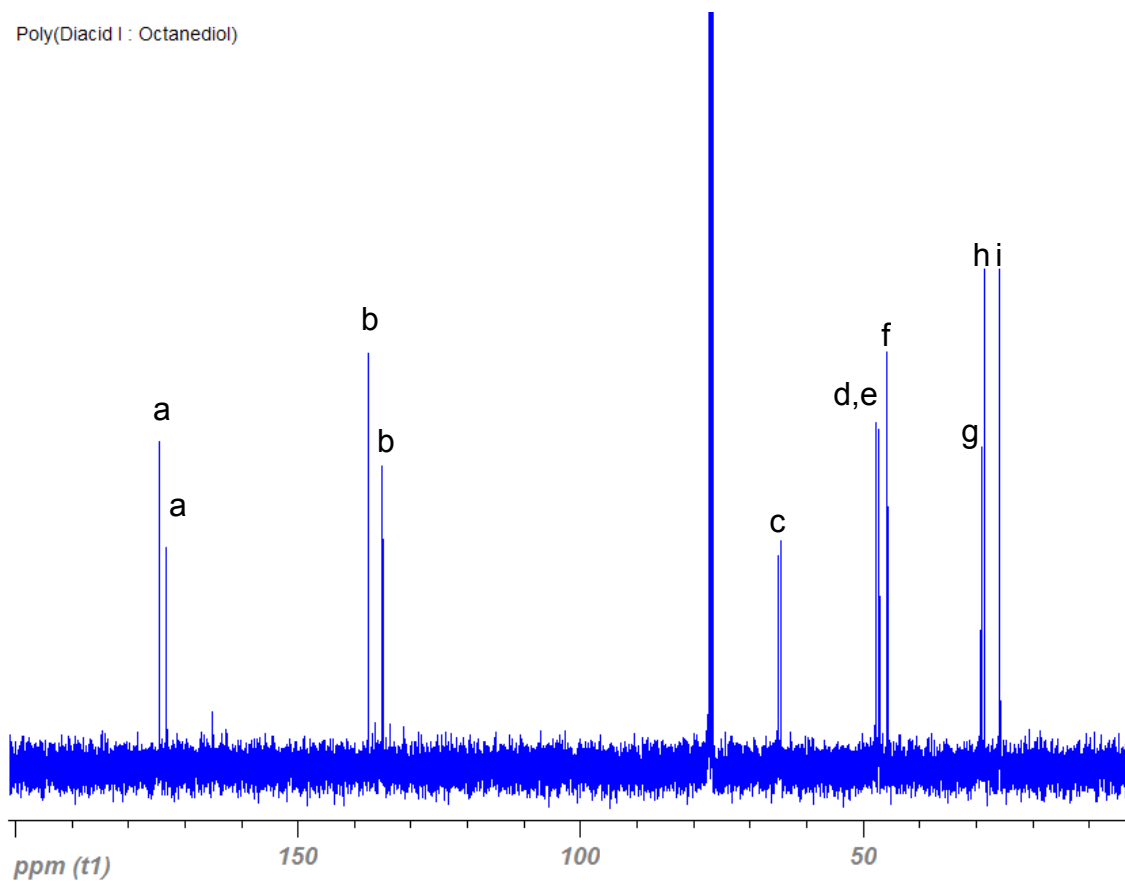
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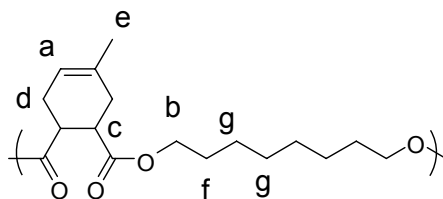
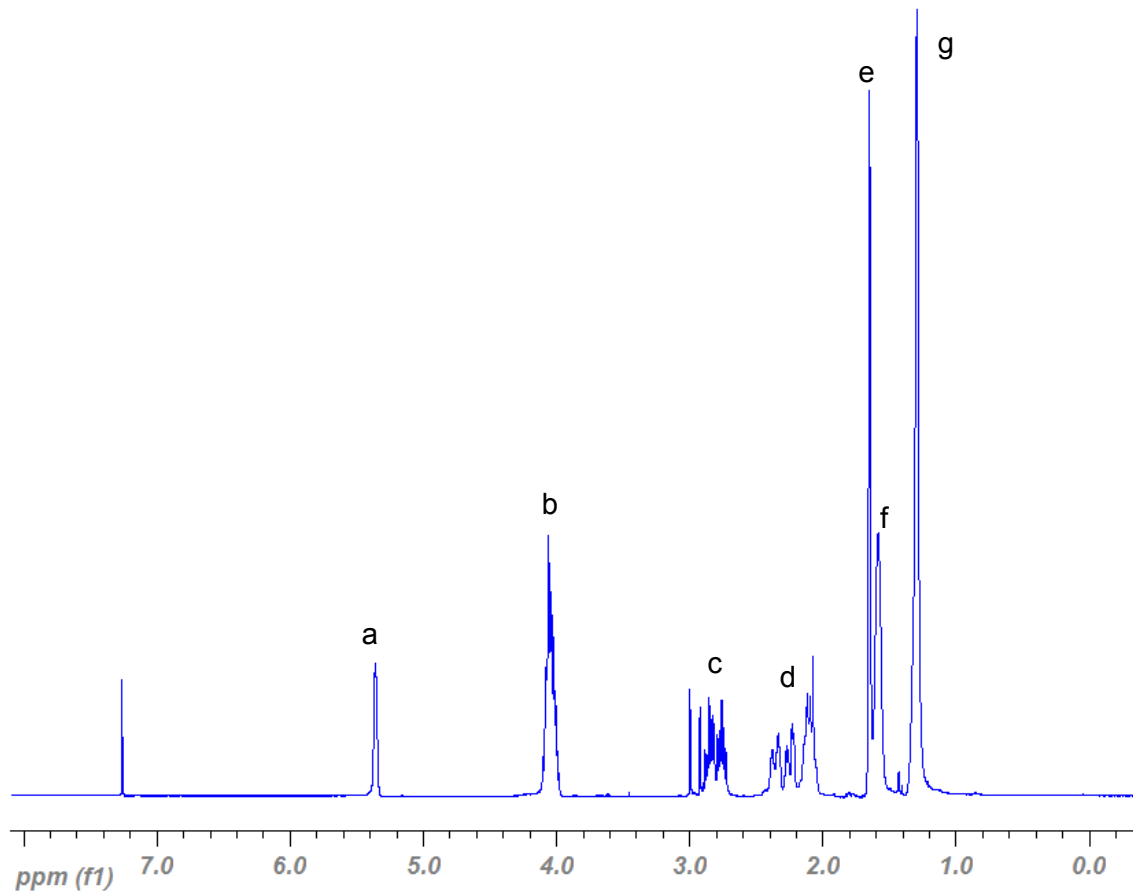
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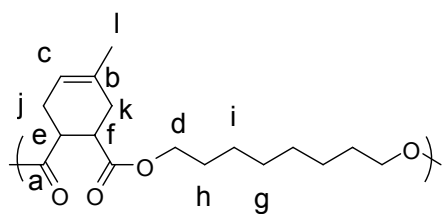
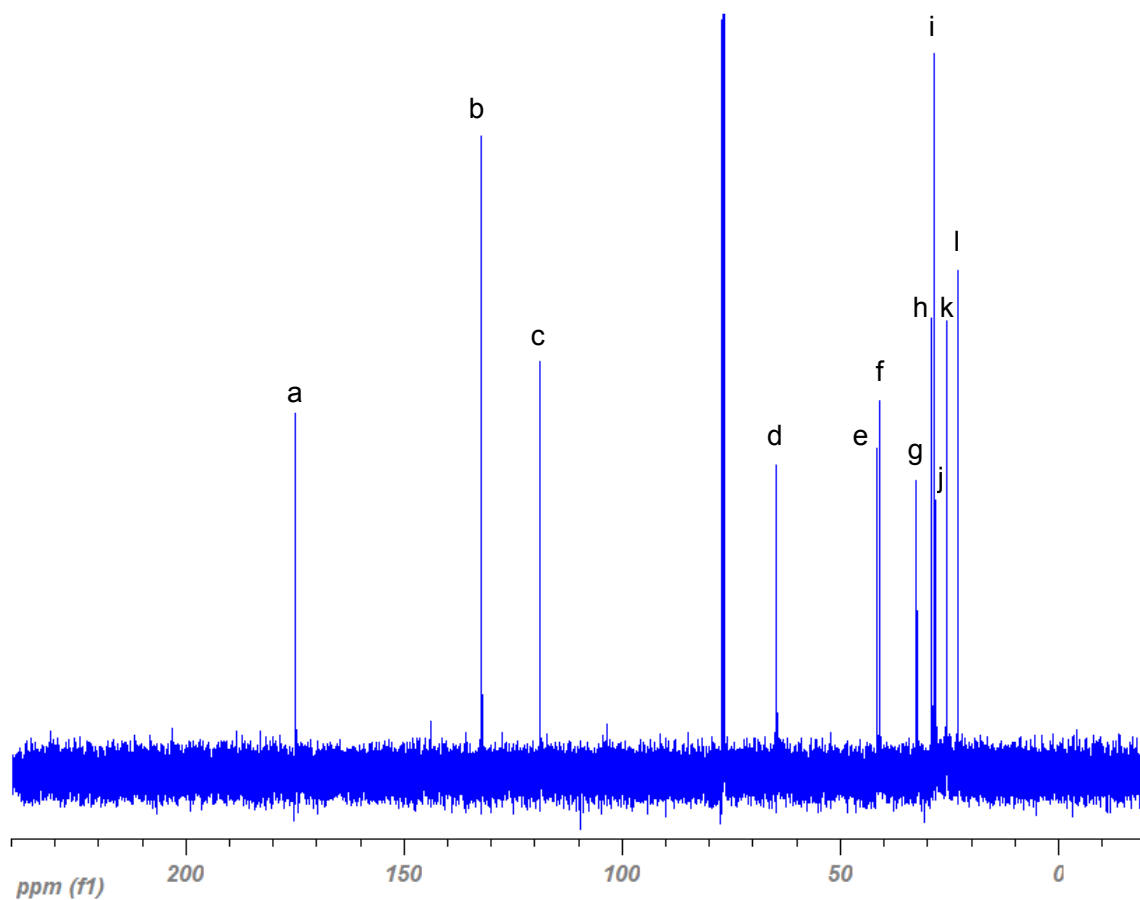
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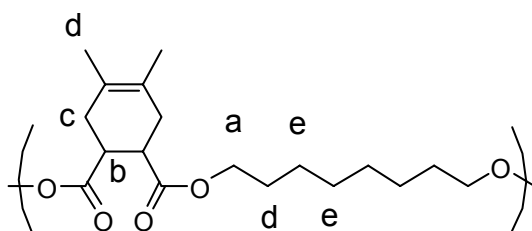
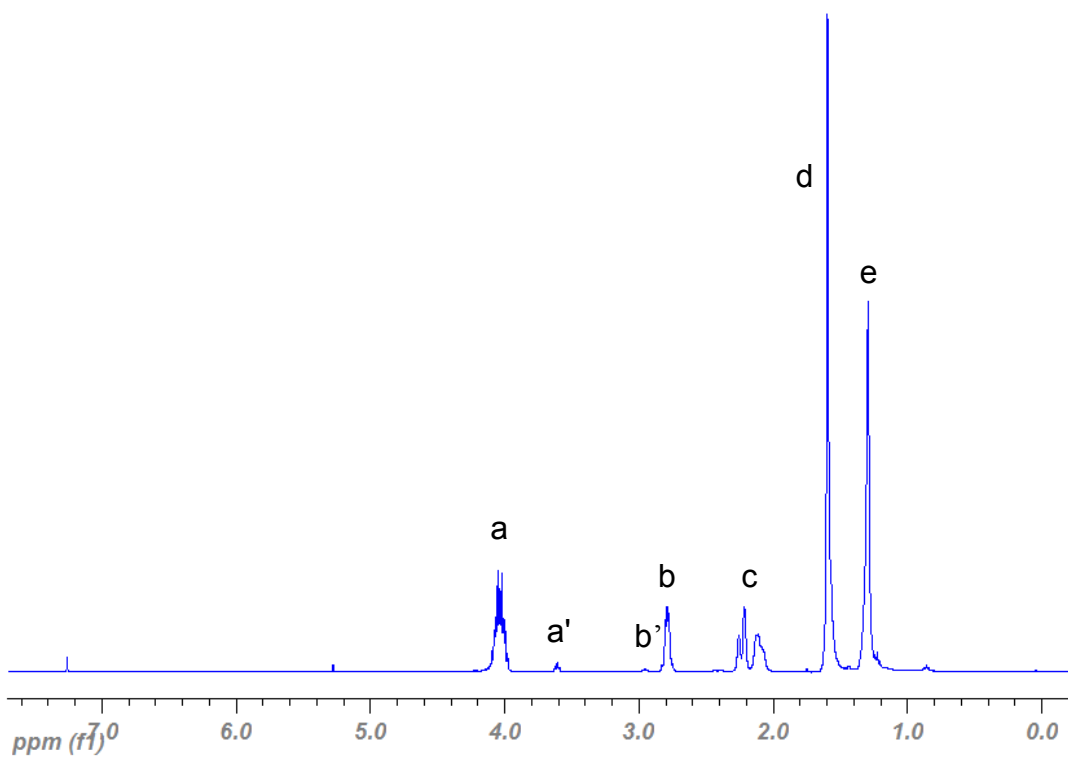
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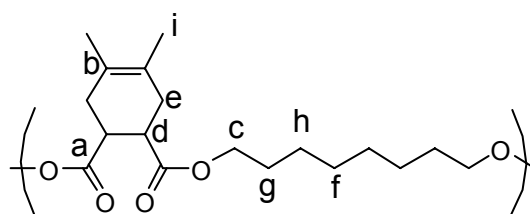
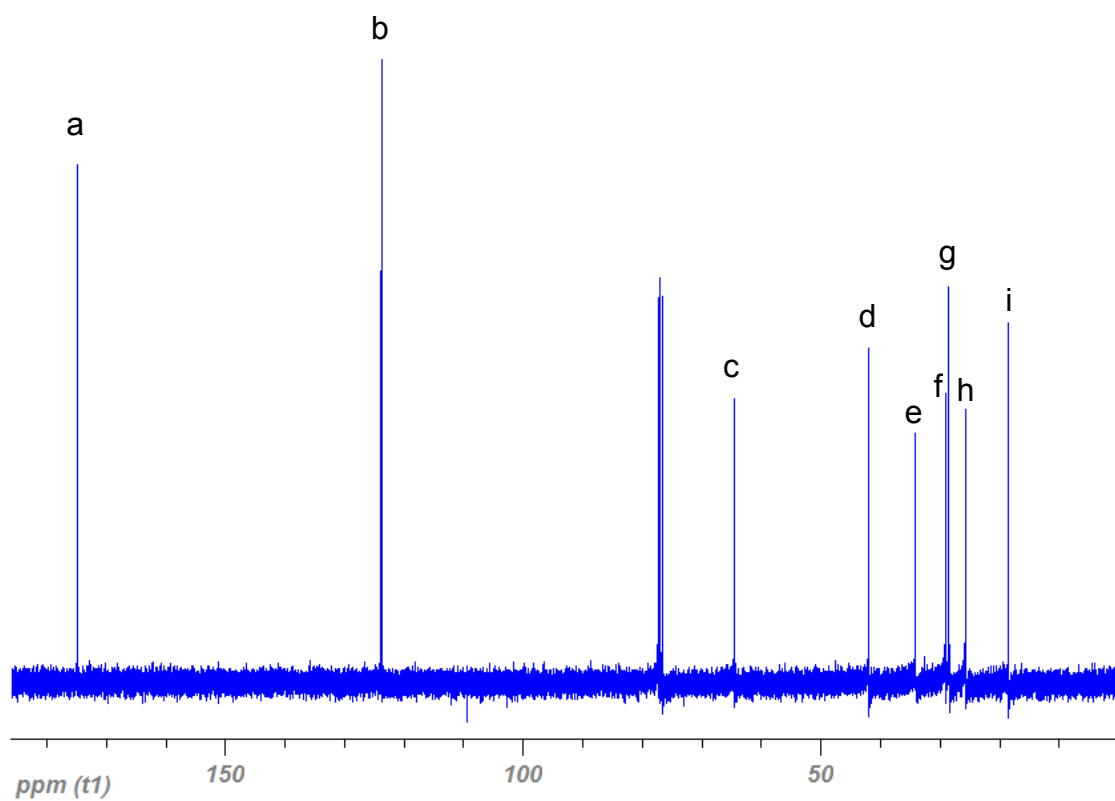
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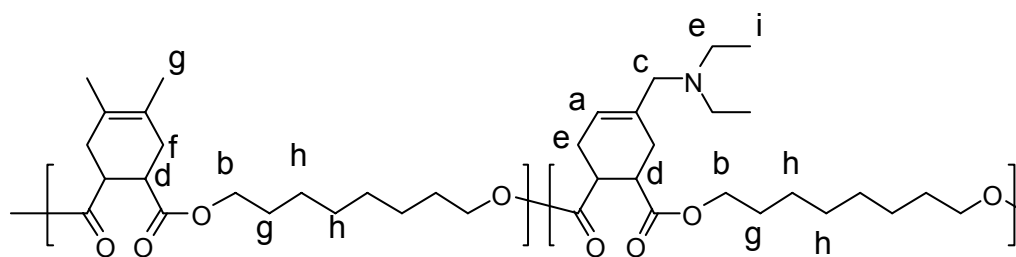
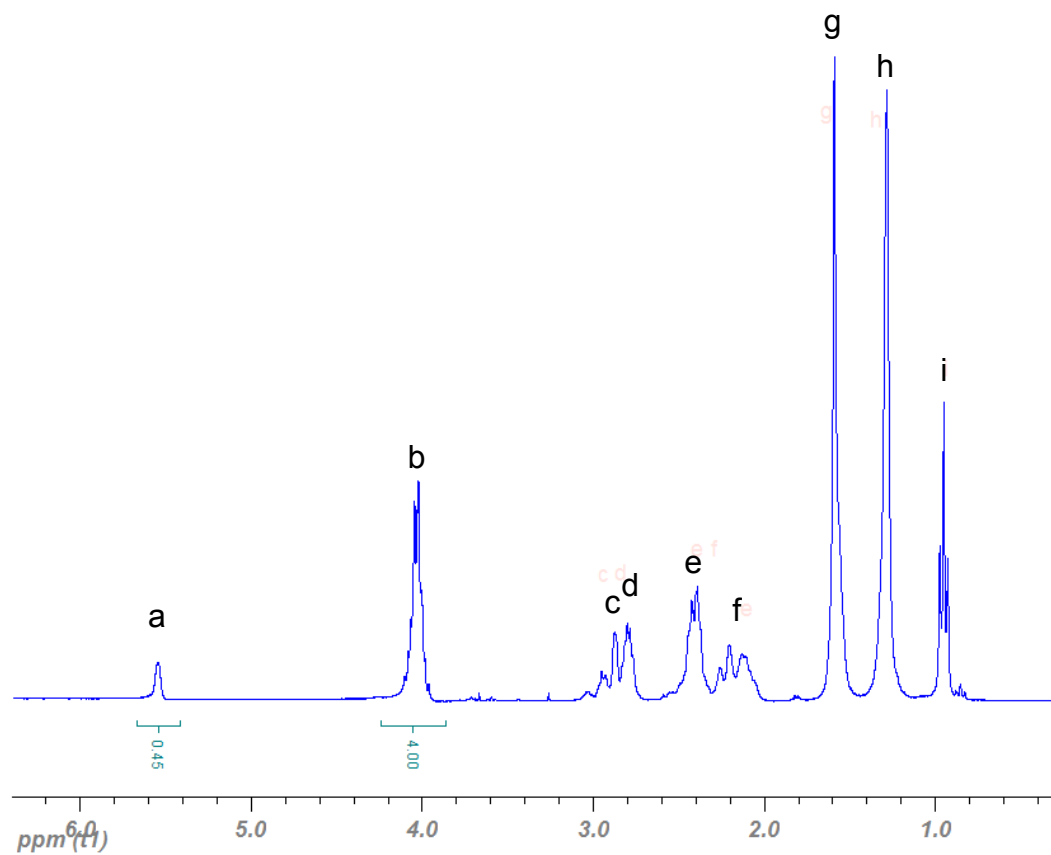
Poly(Diacid III : Octanediol)



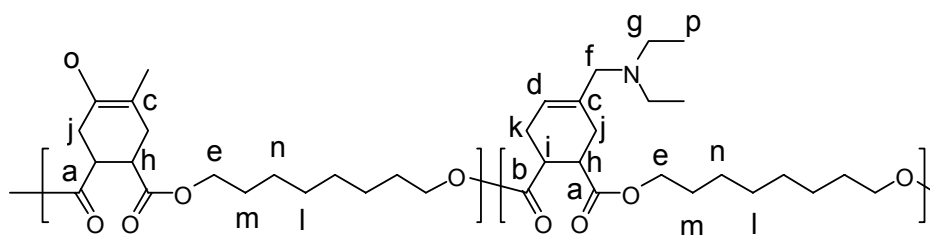
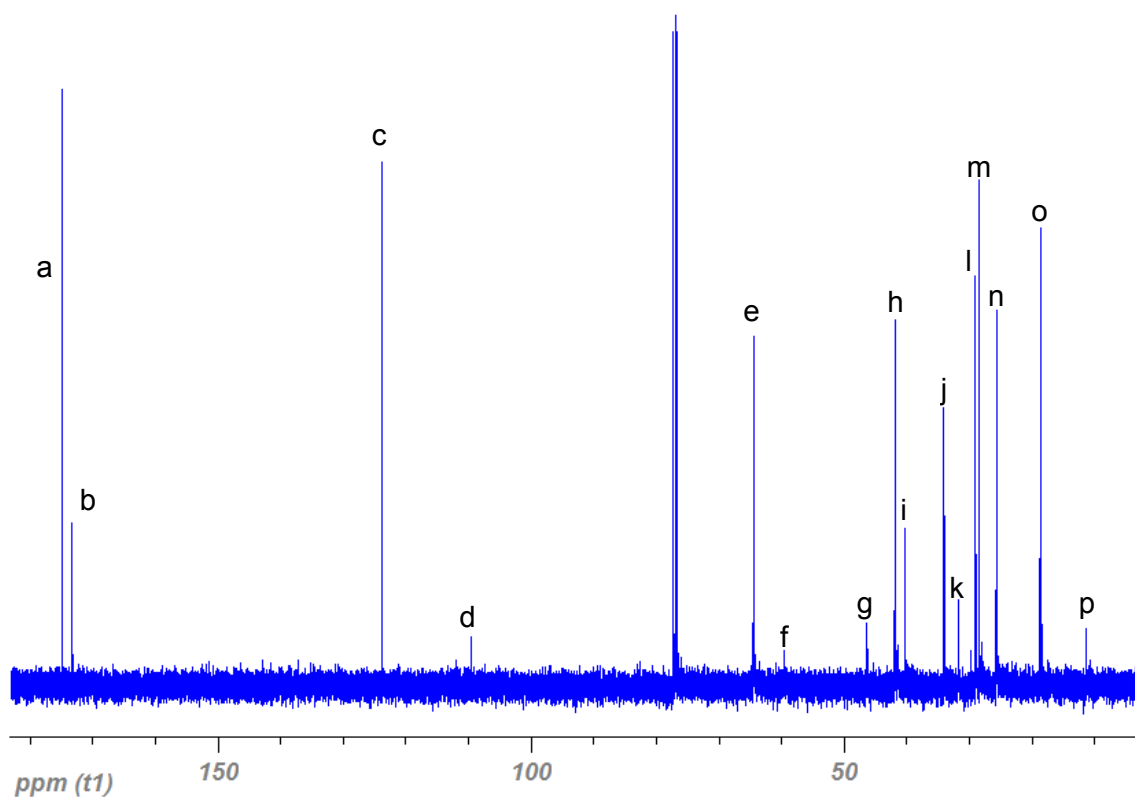
Poly(Diacid III : Octanediol)



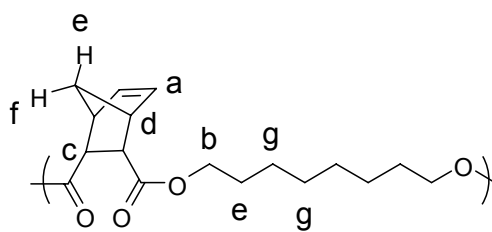
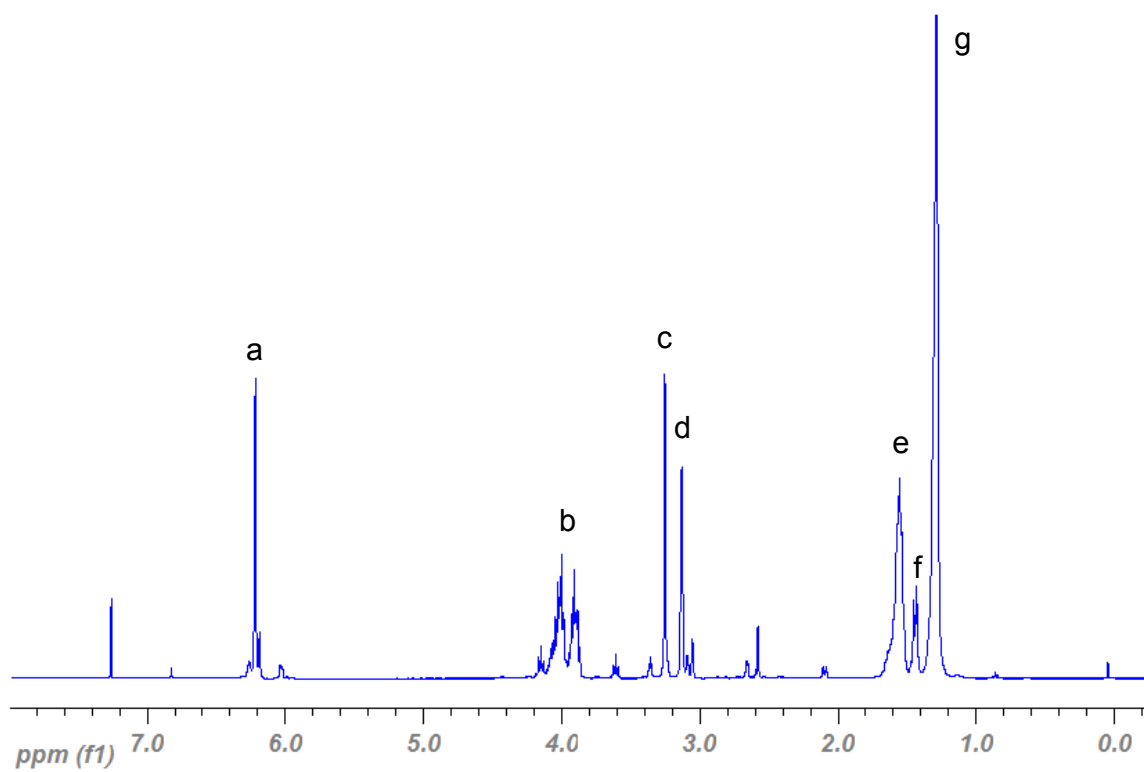
50:50 Copolymer of Diacid III and Diacid IV with Octanediol



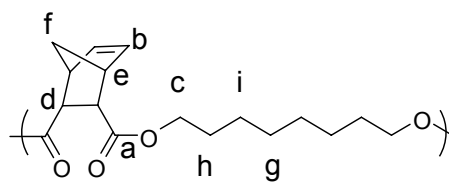
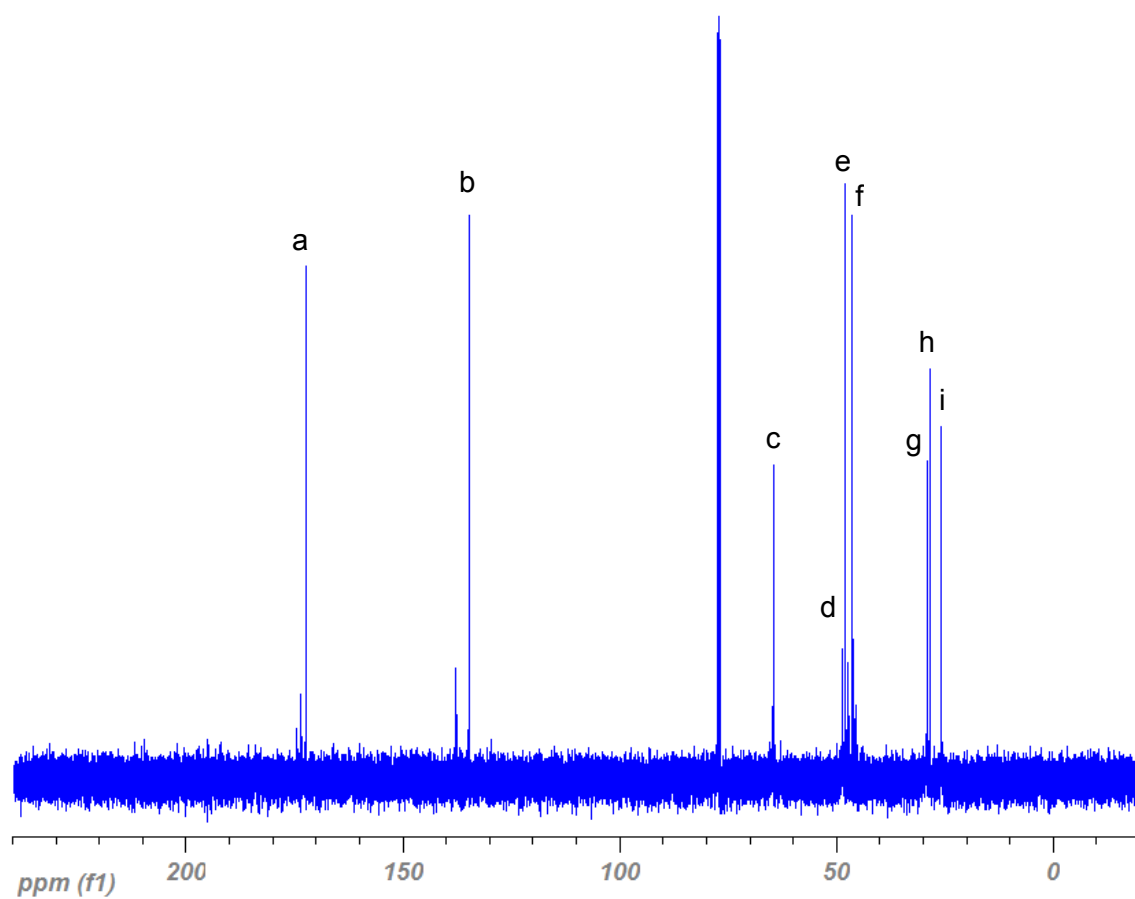
80:20 Copolymer of Diacid III and Diacid IV with Octanediol



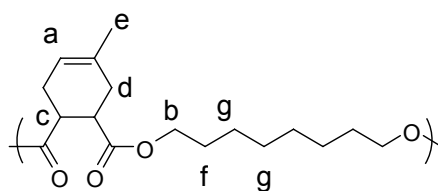
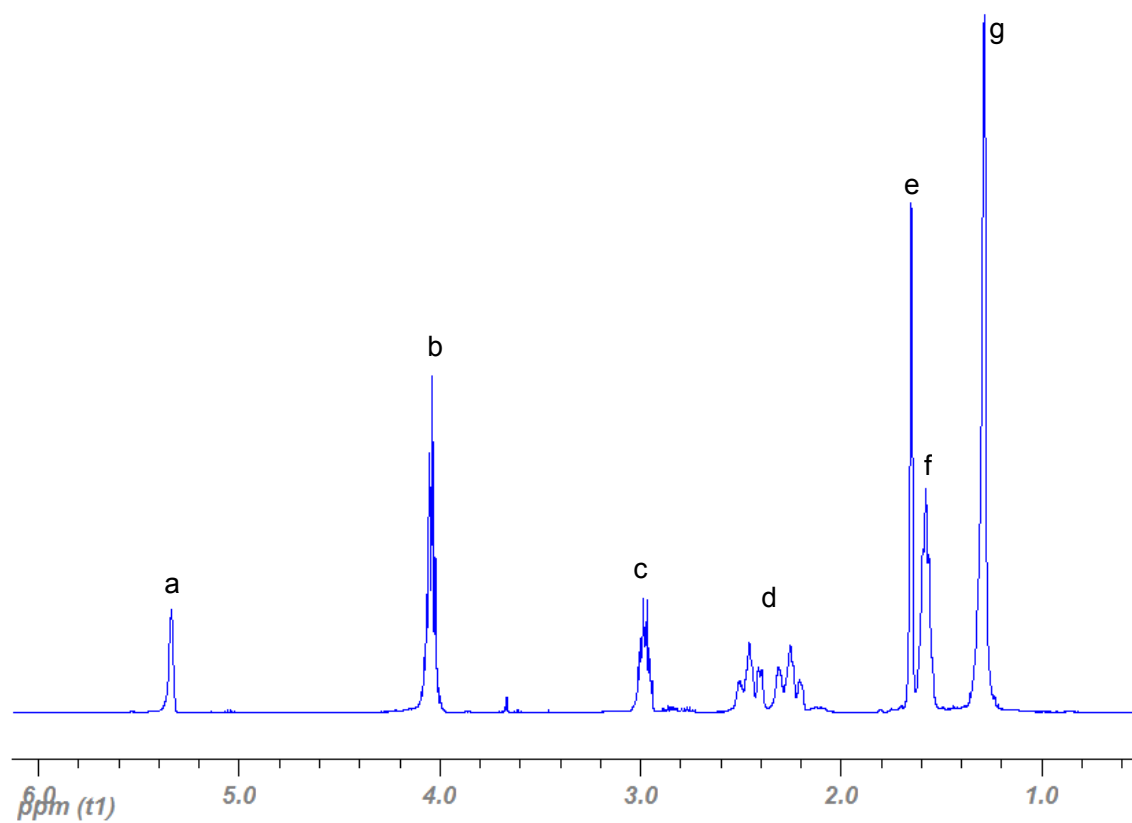
Poly(Anhydride I : Octanediol)



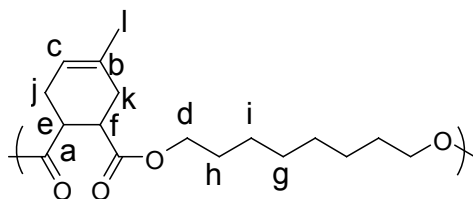
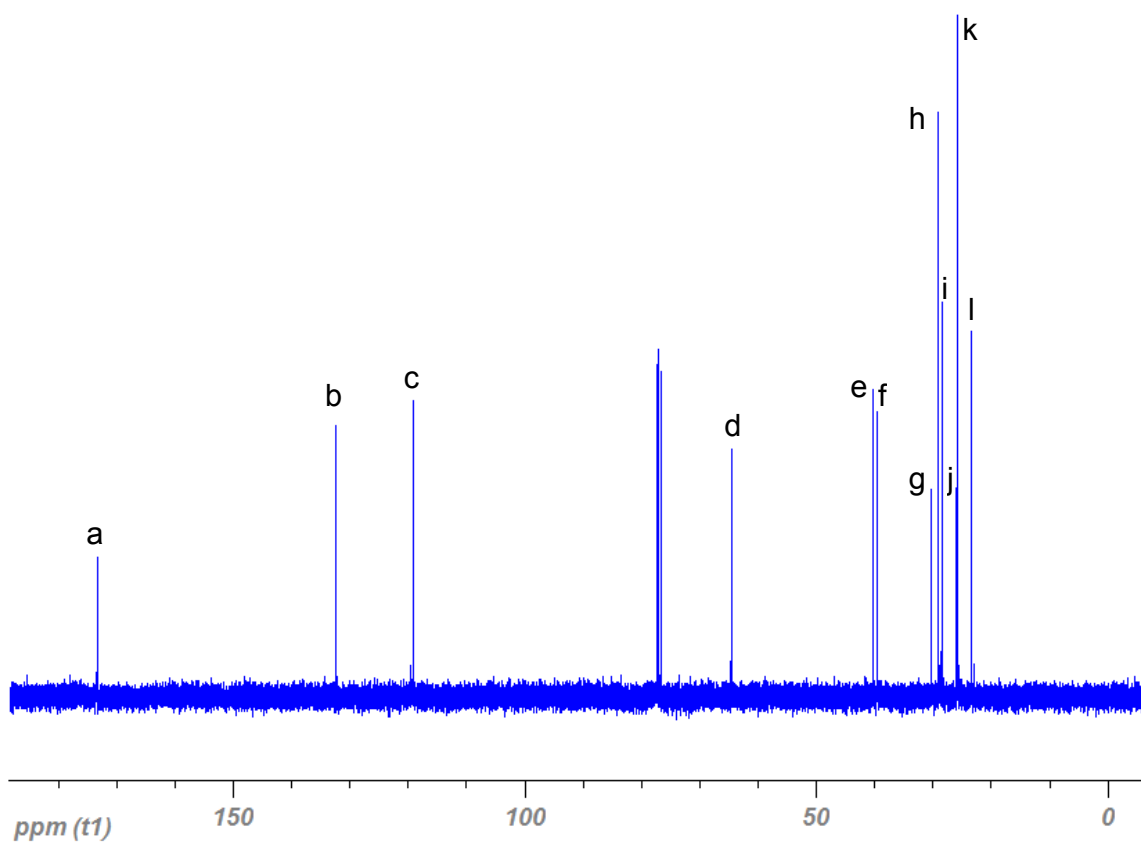
Poly(Anhydride I : Octanediol)



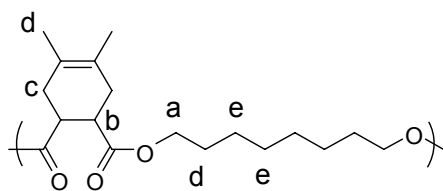
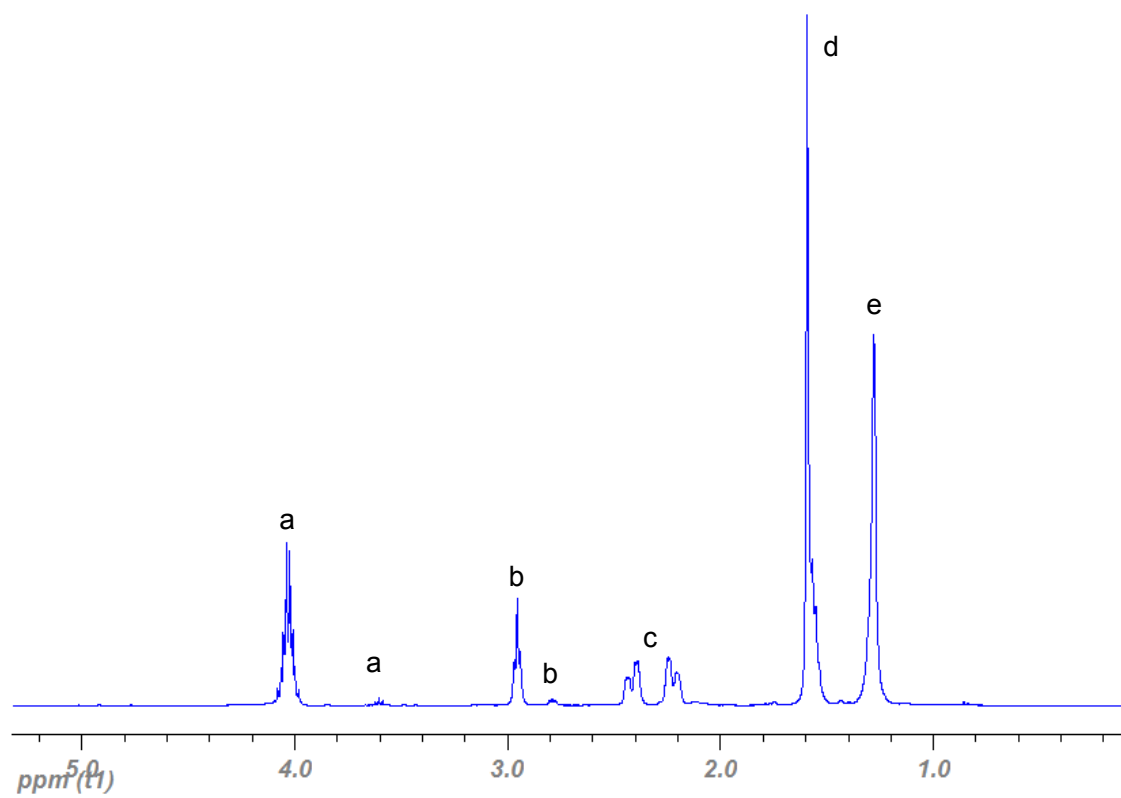
Poly(Anhydride II : Octanediol)



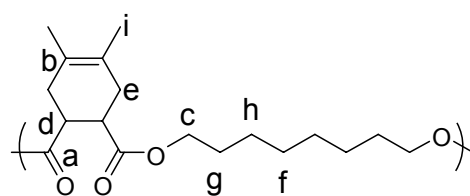
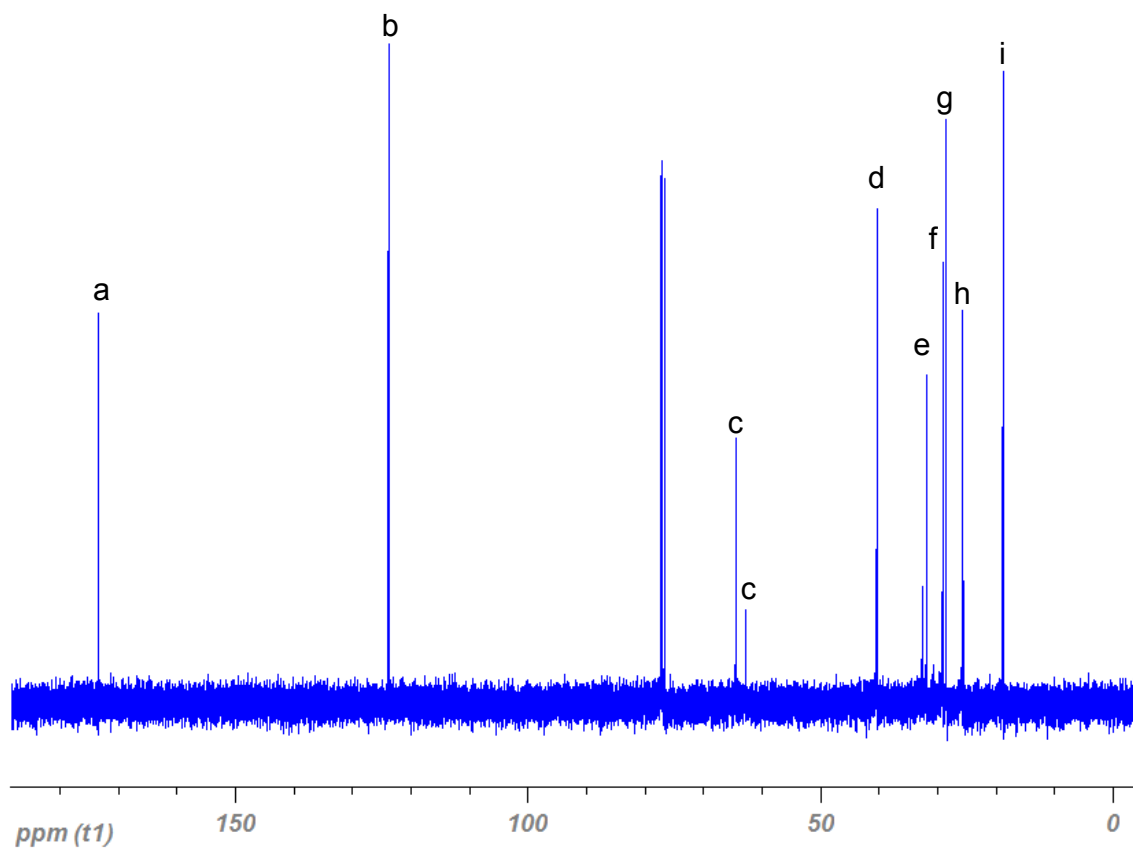
Poly(Anhydride II : Octanediol)



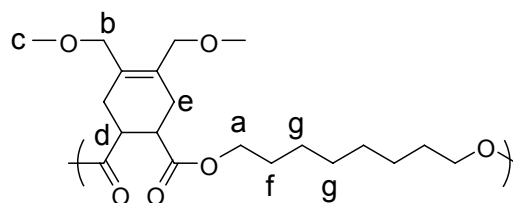
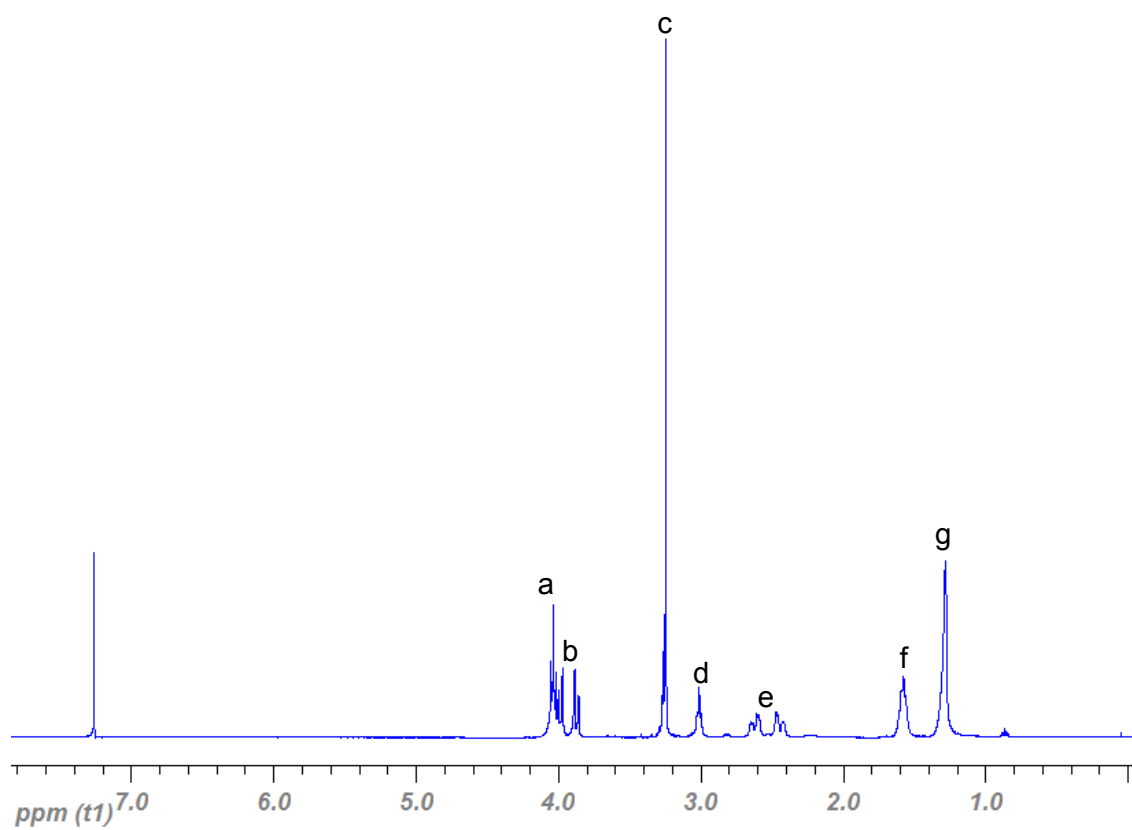
Poly(Anhydride III : Octanediol)



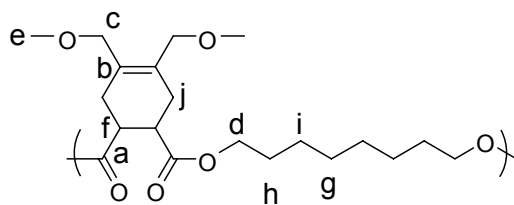
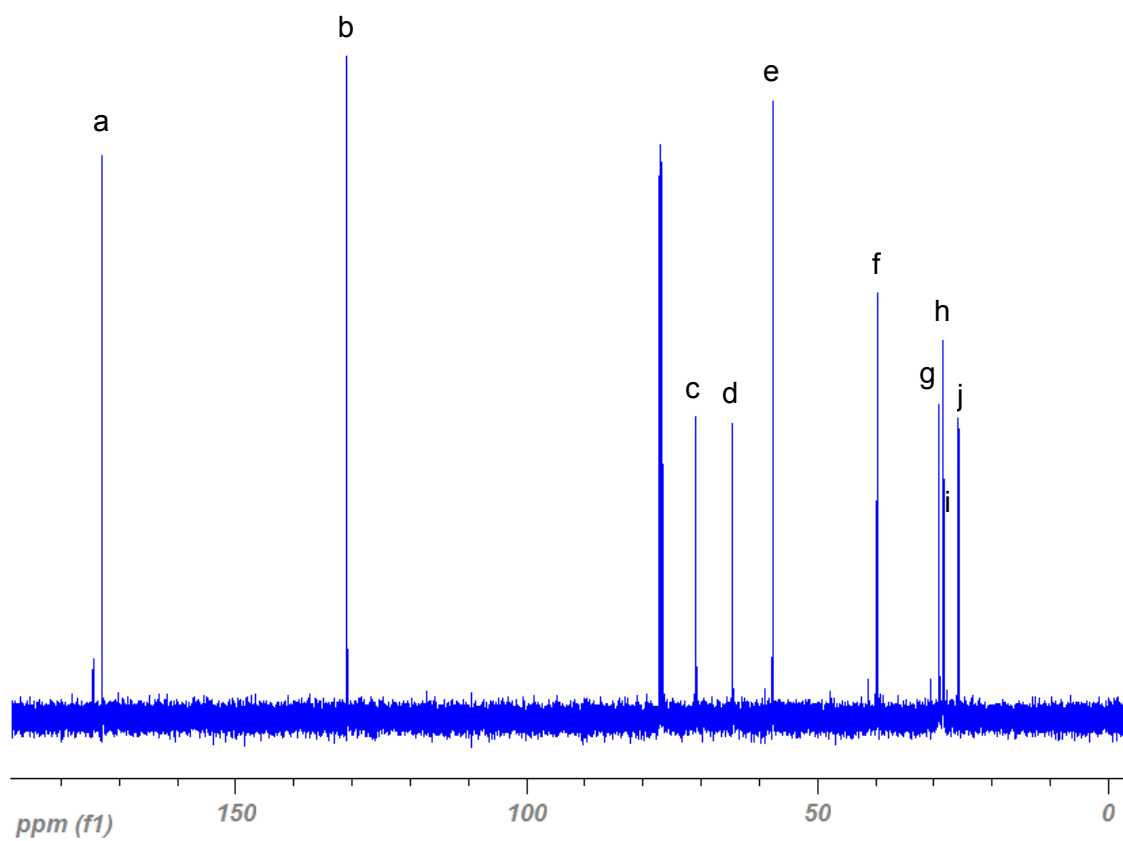
Poly(Anhydride III : Octanediol)



Poly(Anhydride V : Octanediol)



Poly(Anhydride V : Octanediol)

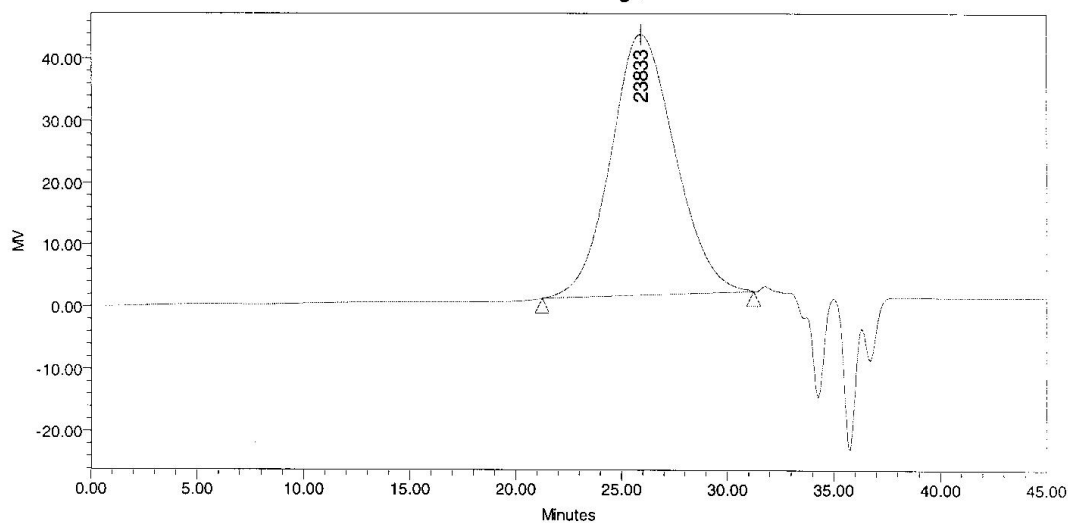


GPC of Polymer 1

SAMPLE INFORMATION

Sample Name:	AB2-04A	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	11/4/05 9:50:41 PM
Vial:	10	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	11/7/05 8:55:26 AM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES 051104	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



GPC Results

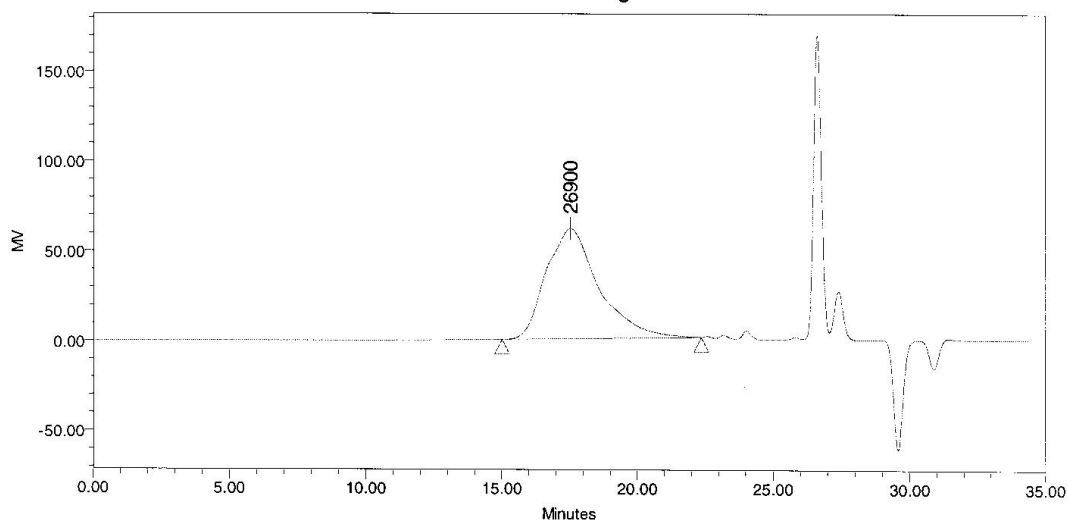
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		14371	28992		23833	51879	85835	2.017352		

GPC of Polymer 2

SAMPLE INFORMATION

Sample Name:	ab3-63b	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	9/3/06 10:41:37 PM
Vial:	51	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	9/4/06 1:38:51 PM
Injection Volume:	150.00 ul	Processing Method:	PM_060823 THF
Run Time:	35.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES_060903	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		16993	30510		26900	47445	67575	1.795419		

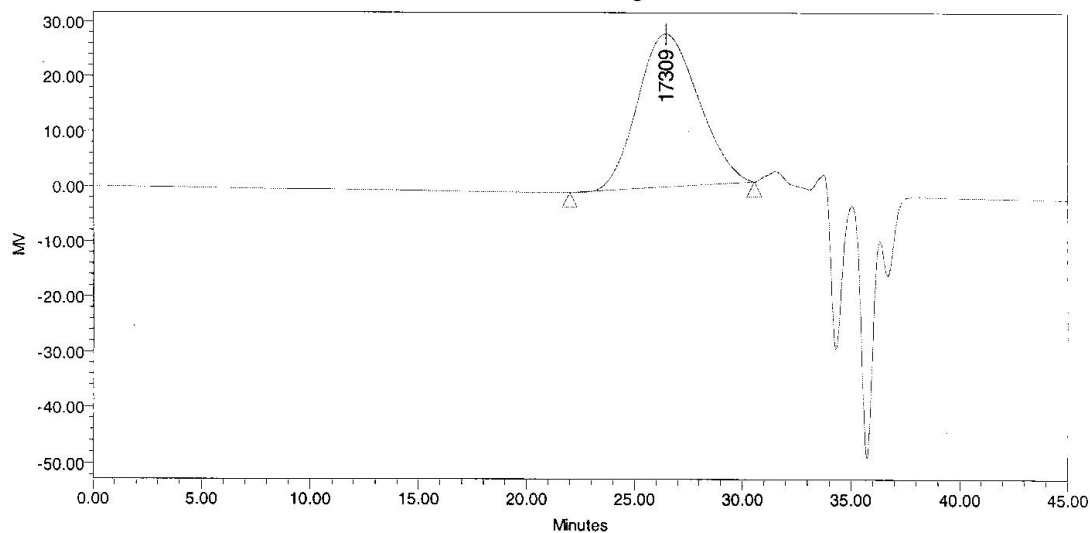
GPC of Polymer 3

Ashby Group GPC

SAMPLE INFORMATION

Sample Name:	AB1-98b	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	11/2/05 8:55:55 PM
Vial:	4	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	11/3/05 8:14:51 AM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	Run_Samples_051102	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



GPC Results

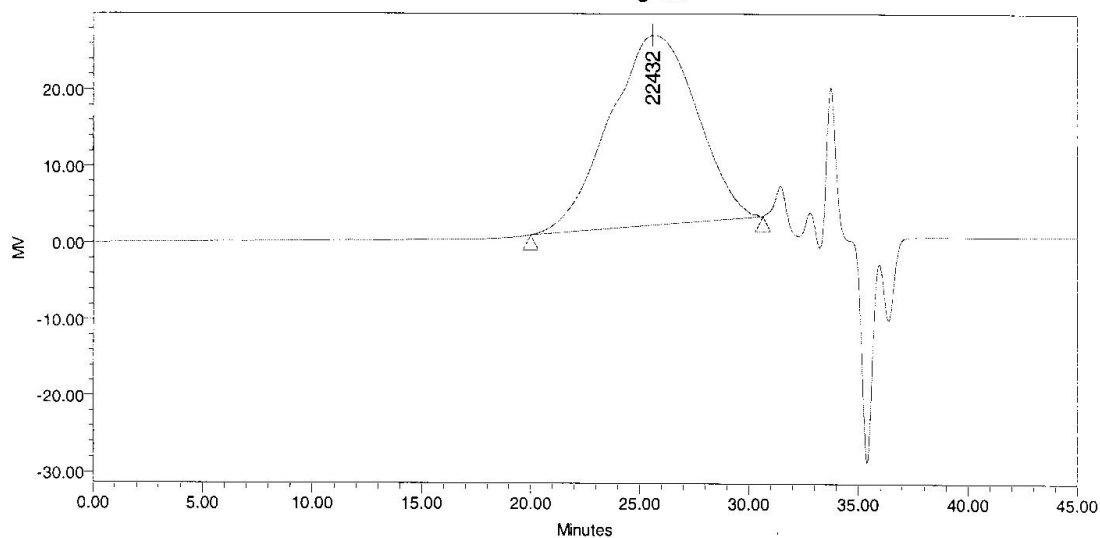
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		11487	19664		17309	29813	40528	1.711863		

GPC of Polymer 4

SAMPLE INFORMATION

Sample Name:	ab3-46d	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	7/24/06 11:03:31 PM
Vial:	66	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	7/25/06 9:20:35 AM
Injection Volume:	150.00 ul	Processing Method:	PM_060614
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	run samples 060724	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		13376	35799		22432	82237	146027	2.676299		

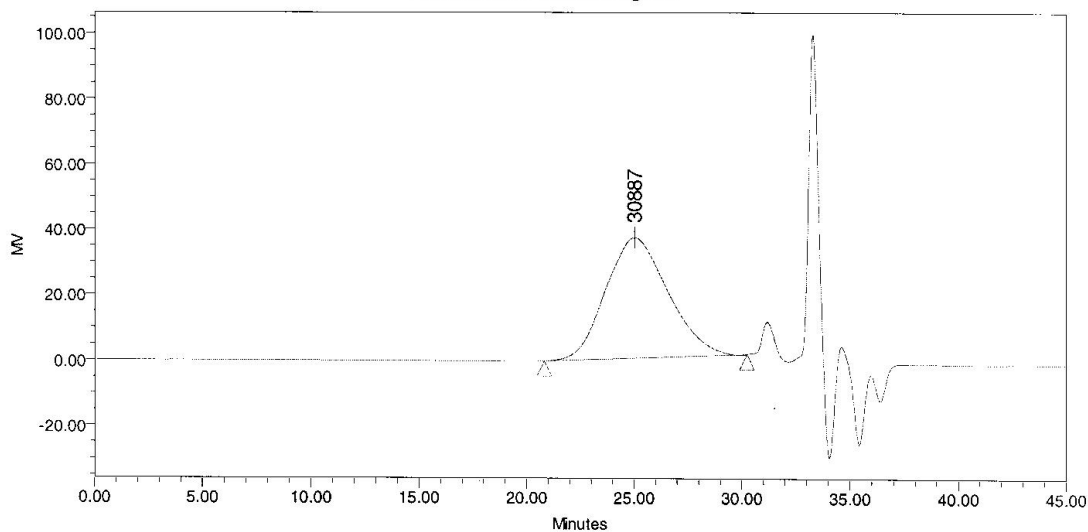
GPC of Polymer 5

SAMPLE INFORMATION

Sample Name: ab3-09B
 Sample Type: Broad Unknown
 Vial: 51
 Injection #: 1
 Injection Volume: 150.00 ul
 Run Time: 45.0 Minutes
 Sample Set Name: run samples 060615

Acquired By: System
 Date Acquired: 6/14/06 7:52:02 PM
 Acq. Method Set: GPCMTHSET
 Date Processed: 6/15/06 7:42:41 AM
 Processing Method: PM_060614
 Channel Name: 410
 Proc. Chnl. Descr.:

Auto-Scaled Chromatogram



GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		20052	35220		30887	54700	77880	1.756476		

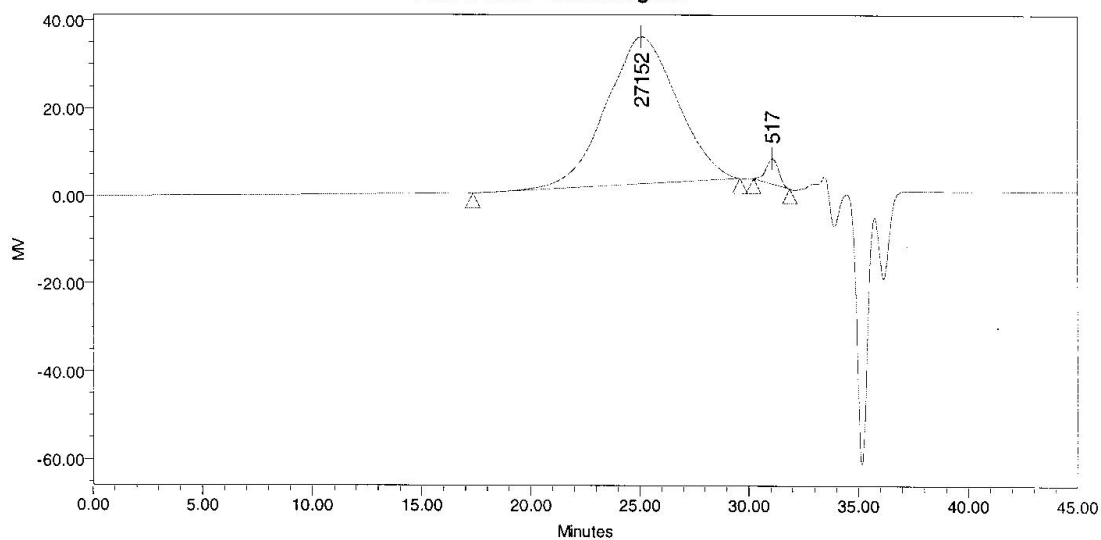
GPC of Polymer 6

SAMPLE INFORMATION

Sample Name: ab2-95A
 Sample Type: Broad Unknown
 Vial: 74
 Injection #: 1
 Injection Volume: 150.00 ul
 Run Time: 45.0 Minutes
 Sample Set Name: RunSamples_060505

Acquired By: System
 Date Acquired: 5/5/06 5:32:49 PM
 Acq. Method Set: GPCMTHSET
 Date Processed: 5/6/06 11:21:51 AM
 Processing Method: PM_060228
 Channel Name: 410
 Proc. Chnl. Descr.:

Auto-Scaled Chromatogram



GPC Results

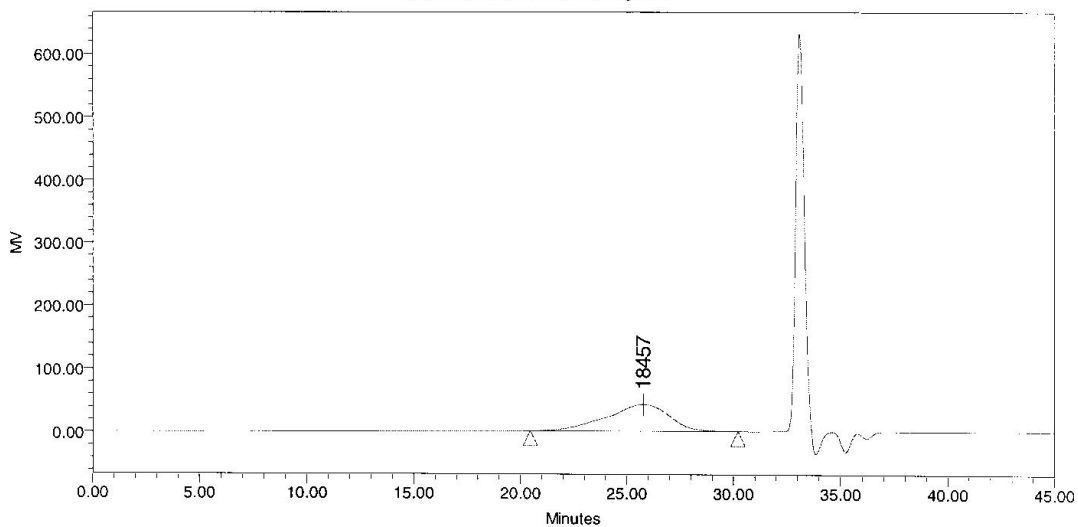
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		18297	39657		27152	93163	227708	2.167439		
2					517					

GPC of Polymer 7

SAMPLE INFORMATION

Sample Name:	AB2-75B	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	3/17/06 2:23:12 PM
Vial:	83	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	3/20/06 9:05:49 AM
Injection Volume:	150.00 ul	Processing Method:	PM_060228
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	run sample 060317	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram

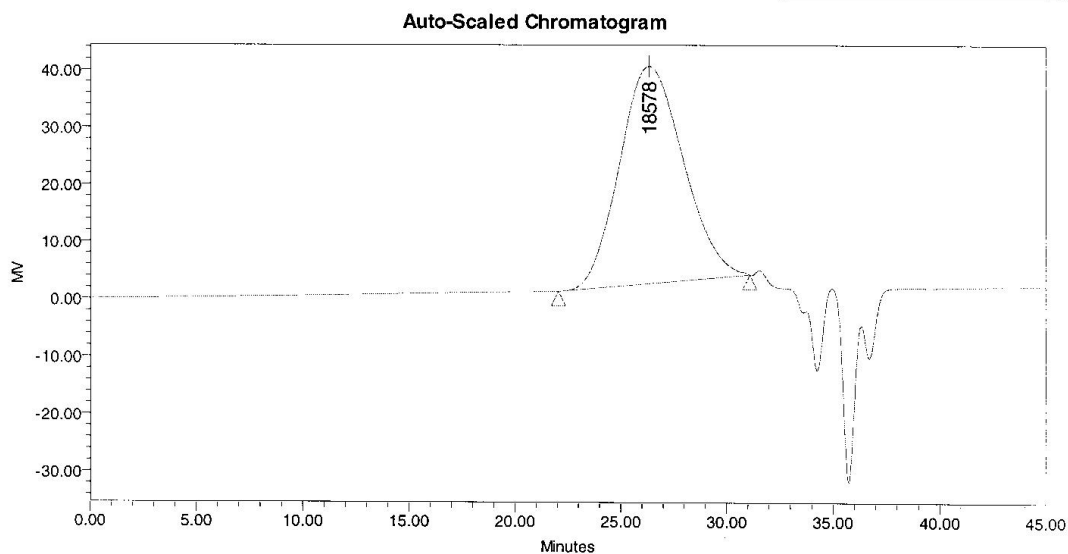


GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		16631	31692		18457	61745	105789	1.905615		

GPC of 90 : 10 Copolymer

SAMPLE INFORMATION			
Sample Name:	AB2-06A	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	11/7/05 4:35:15 PM
Vial:	16	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	11/7/05 6:16:23 PM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES 051107	Proc. Chnl. Descr.:	



GPC Results

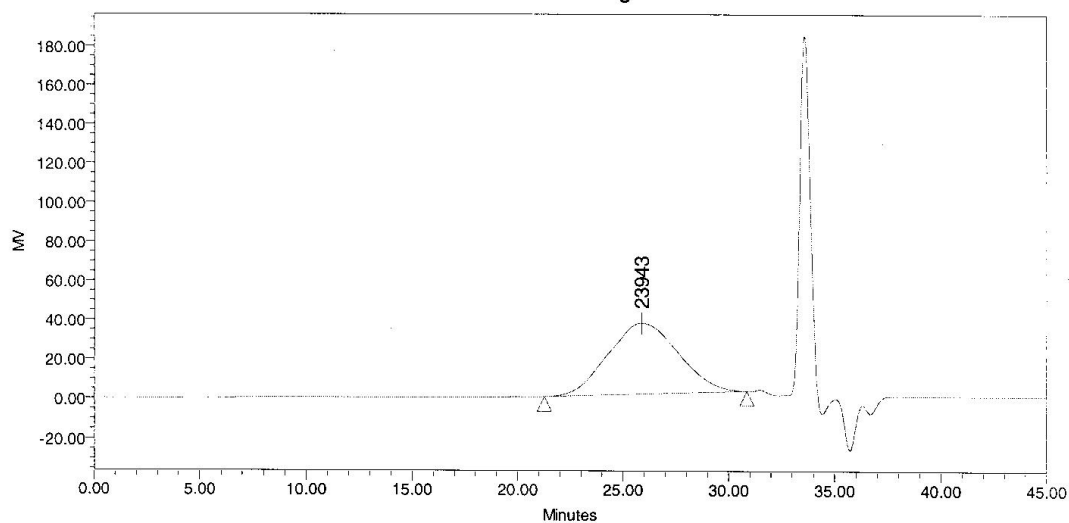
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		11398	21755		18578	35094	49834	1.908706		

GPC of 80 : 20 Copolymer

SAMPLE INFORMATION

Sample Name:	AB2-18B	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	12/5/05 7:45:40 PM
Vial:	50	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	12/6/05 8:45:01 AM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES 051205	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



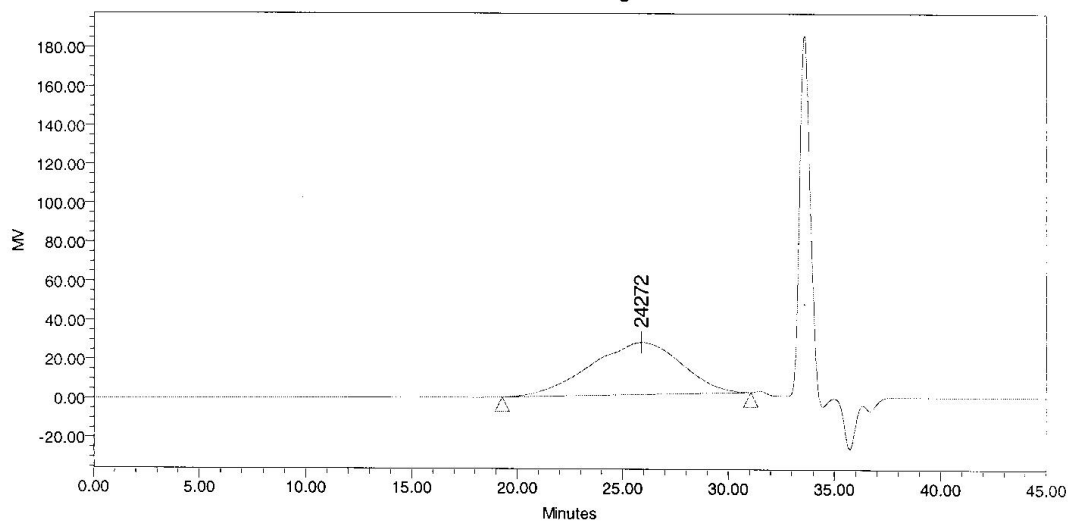
GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		14975	31041		23943	55195	84110	2.072782		

GPC of 70 : 30 Copolymer

SAMPLE INFORMATION			
Sample Name:	AB2-19A	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	12/5/05 8:33:59 PM
Vial:	51	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	12/6/05 8:43:33 AM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES 051205	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



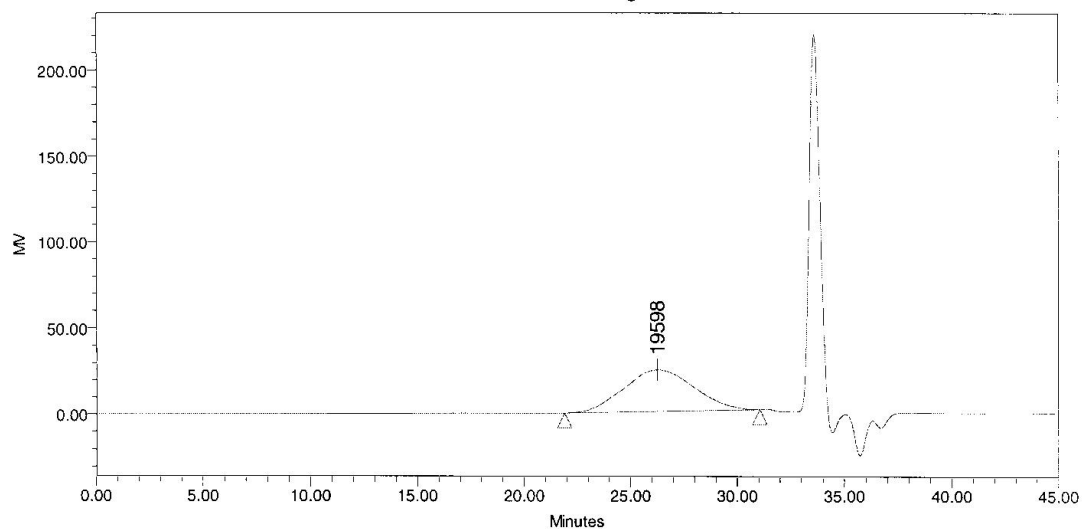
GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		16174	53372		24272	154243	306843	3.299878		

GPC of 60 : 40 Copolymer

SAMPLE INFORMATION			
Sample Name:	AB2-23B	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	12/13/05 5:07:09 PM
Vial:	32	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	12/14/05 10:53:09 AM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES 051213	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



GPC Results

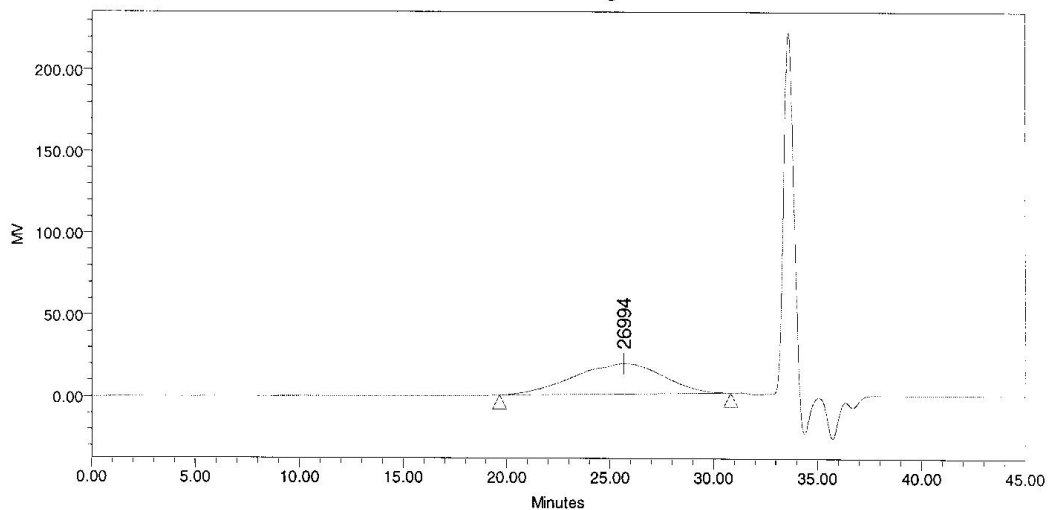
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		12061	25069		19598	43991	65503	2.078470		

GPC of 50 : 50 Copolymer

SAMPLE INFORMATION

Sample Name:	AB2-28A	Acquired By:	System
Sample Type:	Broad Unknown	Date Acquired:	12/13/05 5:55:31 PM
Vial:	33	Acq. Method Set:	GPCMTHSET
Injection #:	1	Date Processed:	12/14/05 10:52:31 AM
Injection Volume:	150.00 ul	Processing Method:	PM_051012
Run Time:	45.0 Minutes	Channel Name:	410
Sample Set Name:	RUN_SAMPLES 051213	Proc. Chnl. Descr.:	

Auto-Scaled Chromatogram



GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		18390	58166		26994	155458	286617	3.162832		

DSC of Polymer 1

<< DSC >>

Data Name: AB2-04A

Date: 5/11/ 8 14:03

Sample: AB2-04A

11.6 mg

Reference: aluminum reference

0 mg

Temperature Program:

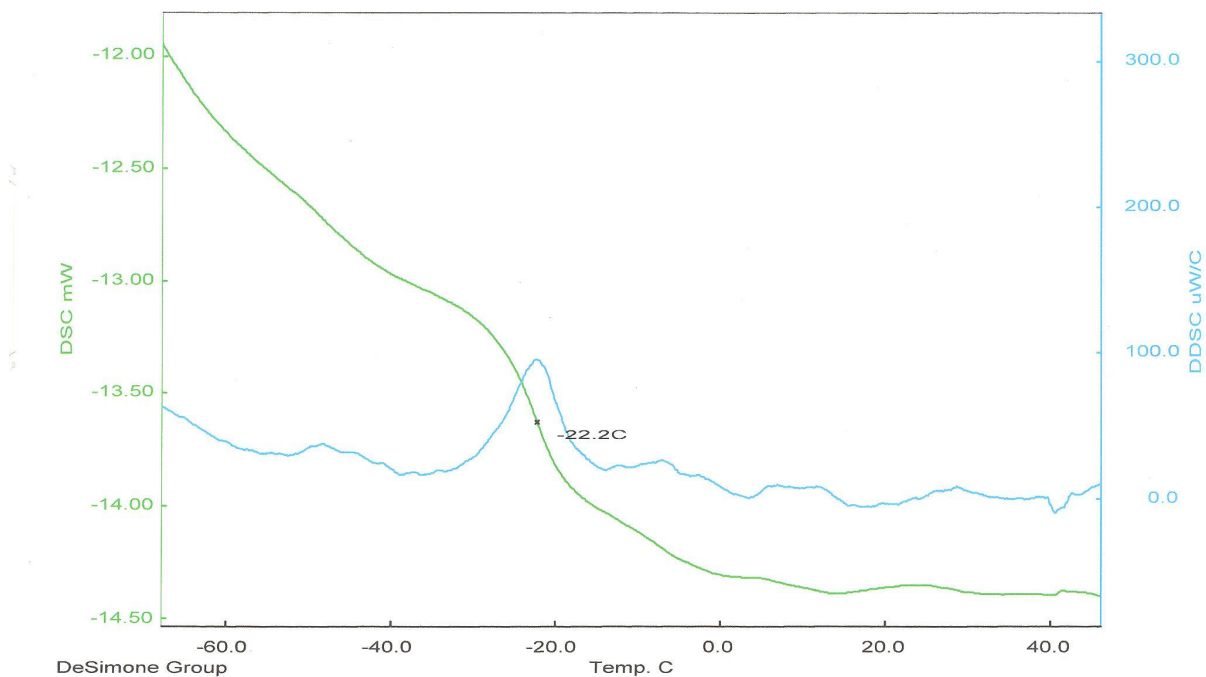
	[C]	[C/min]	[min]	[sec]
1*	25 -	-100	20	10 0.5
2*	-100 -	60	10	5 0.5
3*	60 -	-100	20	10 0.5
4*	-100 -	60	10	1 0.5
5	60 -	25	50	1 0.5

Comments:

Operator Brown

Polyester - NBDA + OD

sealed pan



DSC of Polymer 2

<< DSC >>

Data Name: AB3-63B2

Date: 6/ 9/ 6 16:28

Sample: AB3-63B

18.9 mg

Reference: aluminum reference

0 mg

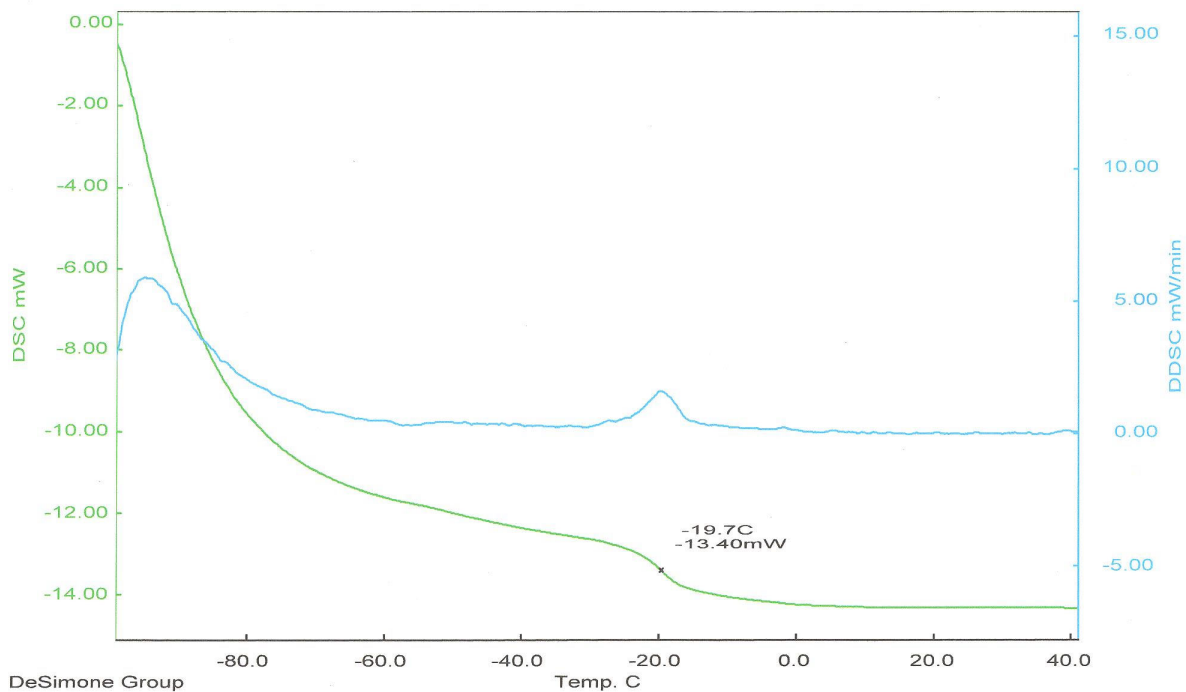
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-100	10	2 0.5
2*	-100	50	10	2 0.5
3*	50	-100	10	5 0.5
4*	-100	50	10	5 0.5
5*	50	-25	25	2 0.5

Comments:

Operator Brown

Polymer 2

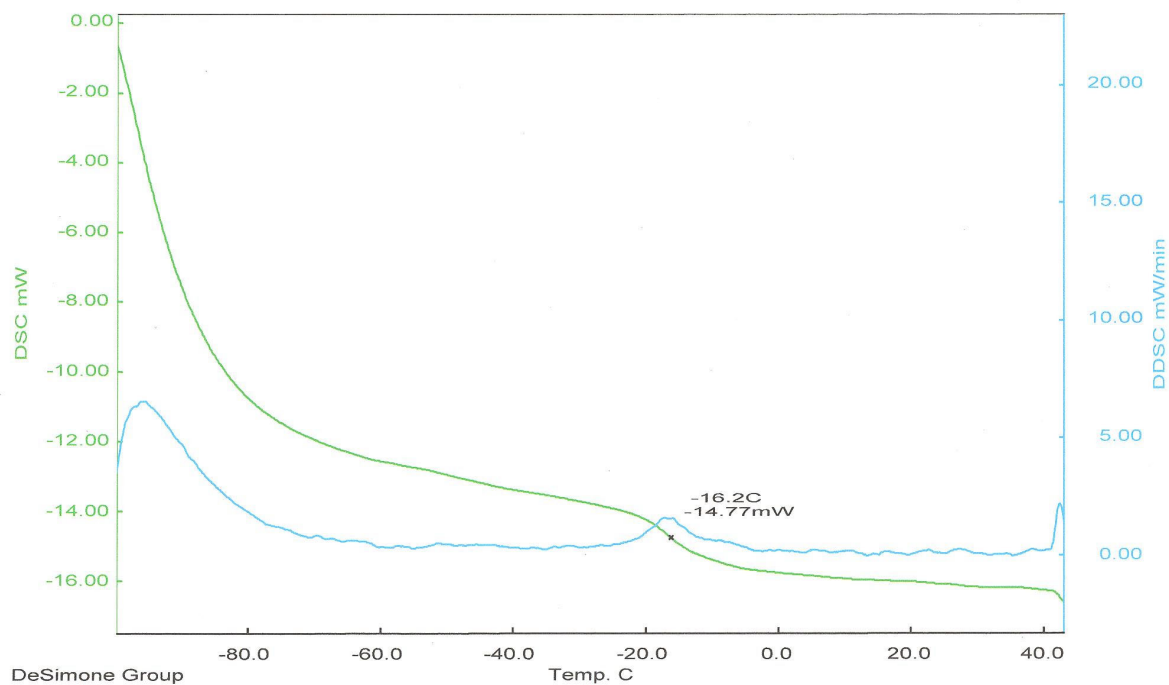


DSC of Polymer 3

<< DSC >>
 Data Name: AB2-02D
 Date: 5/11/10 23:37
 Sample: AB2-02D
 Reference: aluminum reference
 9.1 mg
 0 mg

Temperature Program:						
	[C]	[C/min]	[min]	[sec]		
1*	25	-100	30	5	0.5	
2*	-100	50	10	5	0.5	
3*	50	-100	20	10	0.5	
4*	-100	50	10	5	0.5	
5	50	25	20	1	0.5	

Comments:
 Operator: Brown
 DMDA:OD copolymer



DSC of Polymer 4

<< DSC >>

Data Name: AB3-46D

Date: 6/ 8/31 15:49

Sample: AB3-46D

25.7 mg

Reference: aluminum reference

0 mg

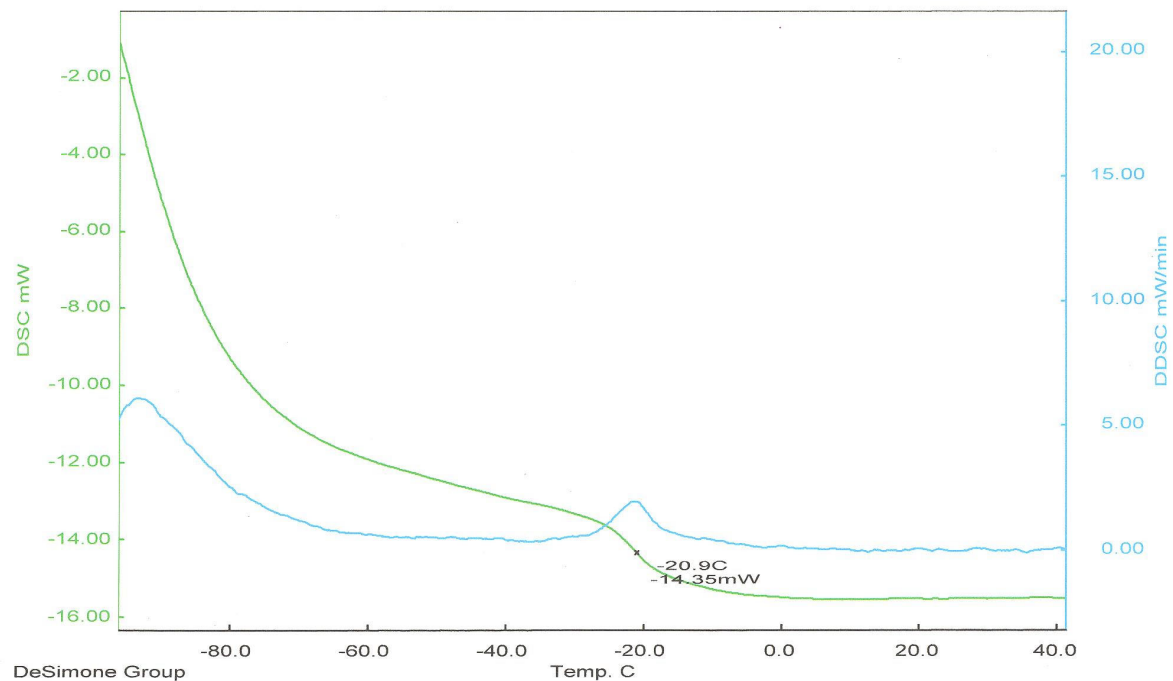
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-100	10	5
2*	-100	50	10	5
3*	50	-100	10	10
4*	-100	50	10	1
5*	50	25	25	1

Comments:

Operator: Brown

AB3-46D Poly(Anh I : OD)



DSC of Polymer 5

<< DSC >>

Data Name: AB3-09B_A

Date: 6/ 9/ 8 10:38

Sample: AB3-09B dried in p

18.9 mg

Reference: aluminum reference

0 mg

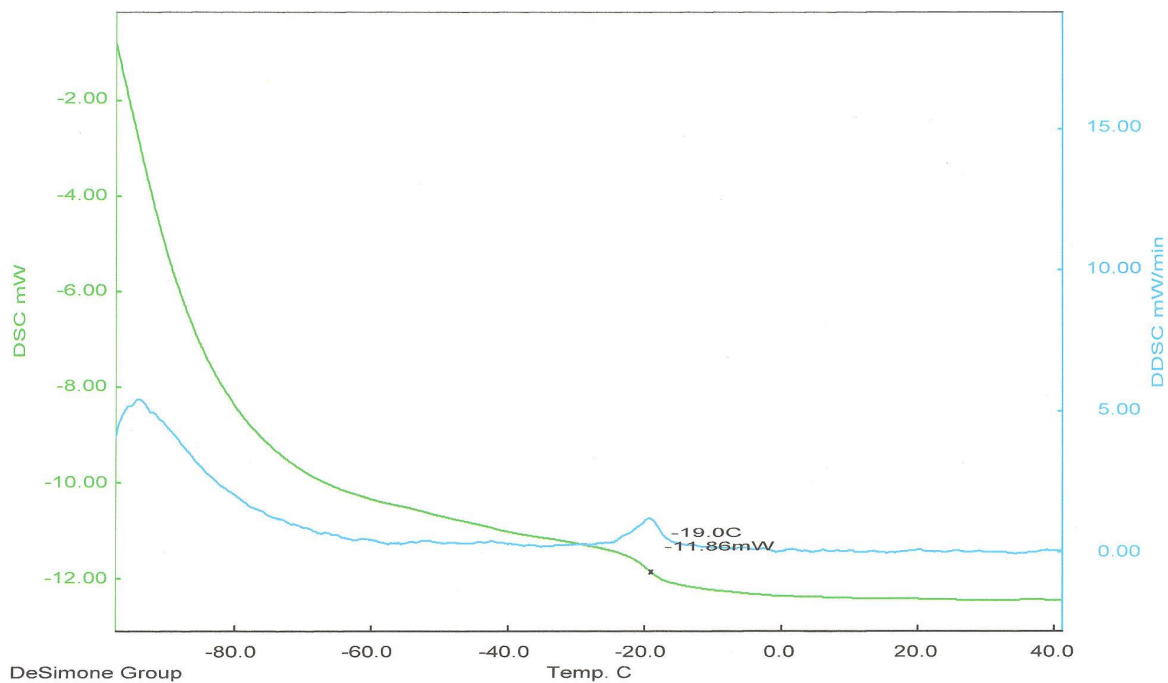
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-100	10	2
2*	-100	50	10	2
3*	50	-100	10	5
4*	-100	50	10	5
5*	50	25	25	2

Comments:

Operator Brown

Polymer 5



DSC of Polymer 6

<< DSC >>

Data Name: AB2-95Adry

Date: 6/ 9/ 1 11:35

Sample: AB2-95A

Reference: aluminum reference

0 mg

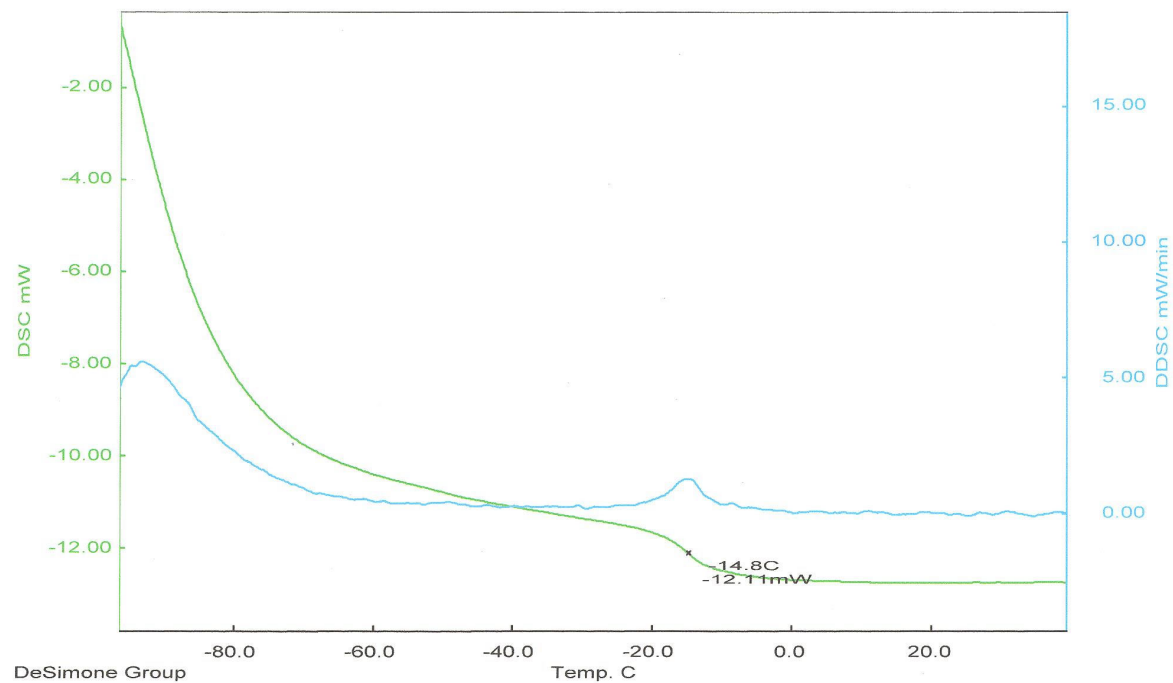
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-100	10	5
2*	-100	50	10	5
3*	50	-100	10	5
4*	-100	50	10	5
5*	50	25	25	2

Comments:

Operator Brown

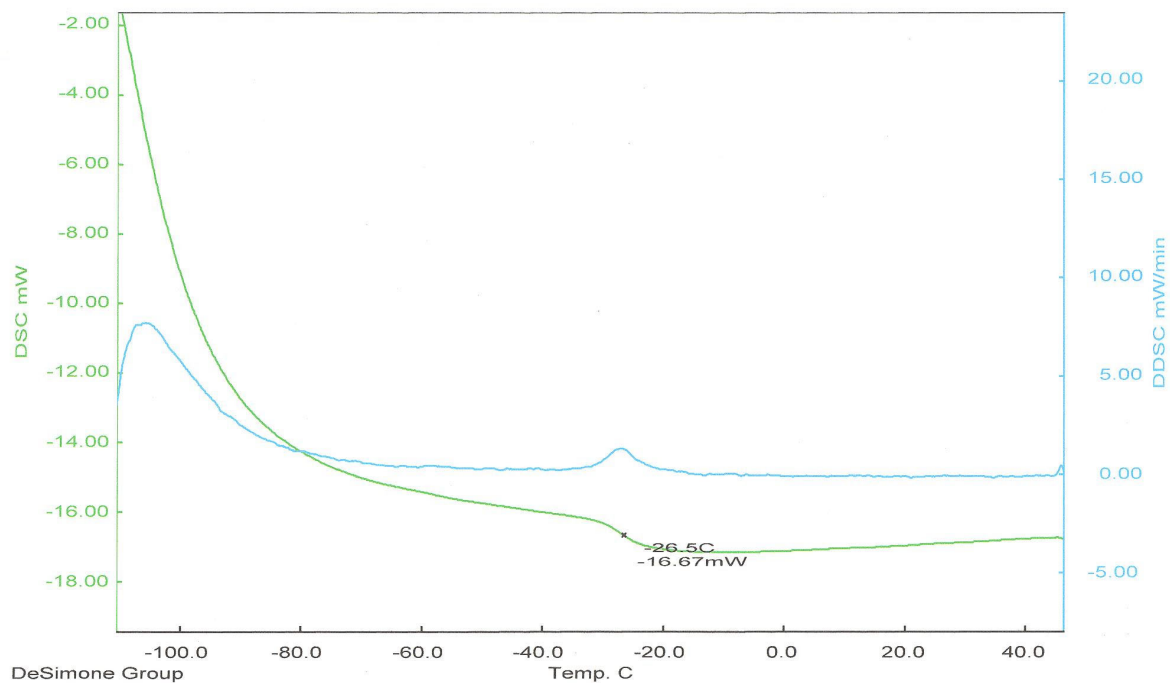
Poly(All:OD)



DSC of Polymer 7

<< DSC >>

Data Name: AB2-75B	Temperature Program:	Comments:
Date: 6/ 3/20 15:34	[C] [C/min] [min] [sec]	Operator: Brown
Sample: AB2-75B	1* 25 - -100 10 5 0.5	AB2-75B homopolymer
	2* -100- 50 10 5 0.5	
	3* 50 - -100 10 10 0.5	
Reference: aluminum reference	4* -100- 50 10 10 0.5	
0 mg	5 50 - 25 40 2 0.5	



DSC of 90 : 10 Copolymer

<< DSC >>

Data Name: AB2-06A-DRIED

Date: 5/11/10 18:01

Sample: AB2-06A

Reference: aluminum reference

0 mg

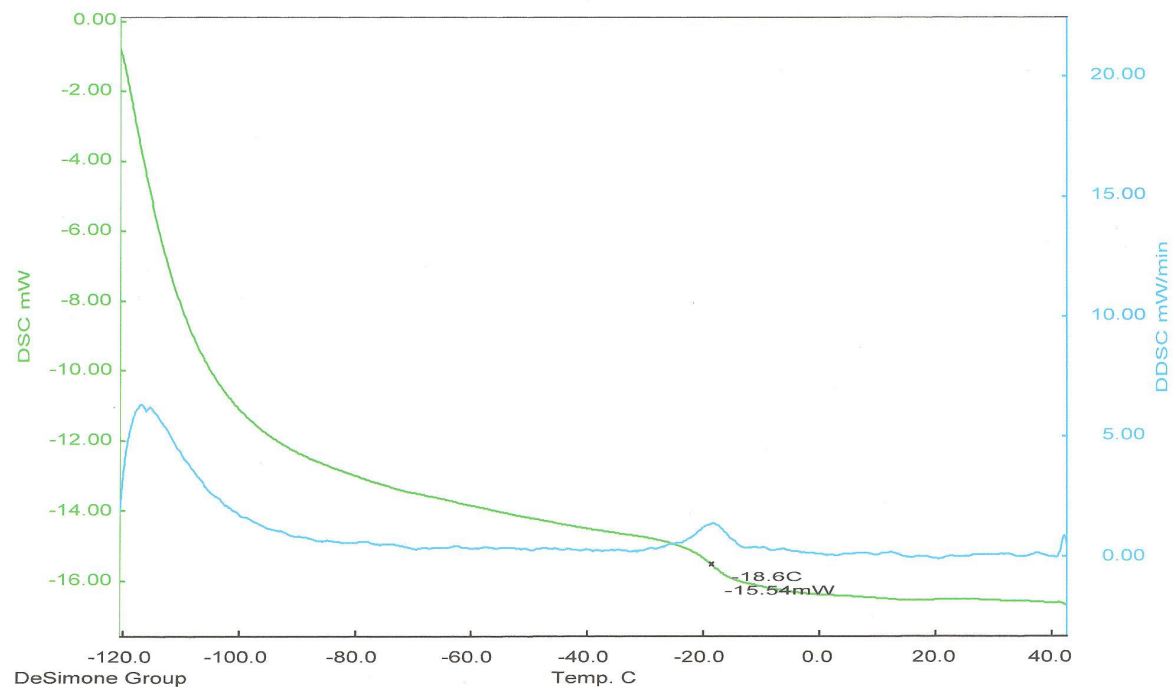
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-120	30	5
2*	-120	50	10	5
3*	50	-120	20	10
4*	-120	50	10	5
5	50	25	20	1

Comments:

Operator: Brown

DMDA:DEADA:OD copolymer



DSC of 80 : 20 Copolymer

<< DSC >>

Data Name: AB2-18B

Date: 5/12/13 11:31

Sample: AB2-18B

5 mg

Reference: aluminum reference

0 mg

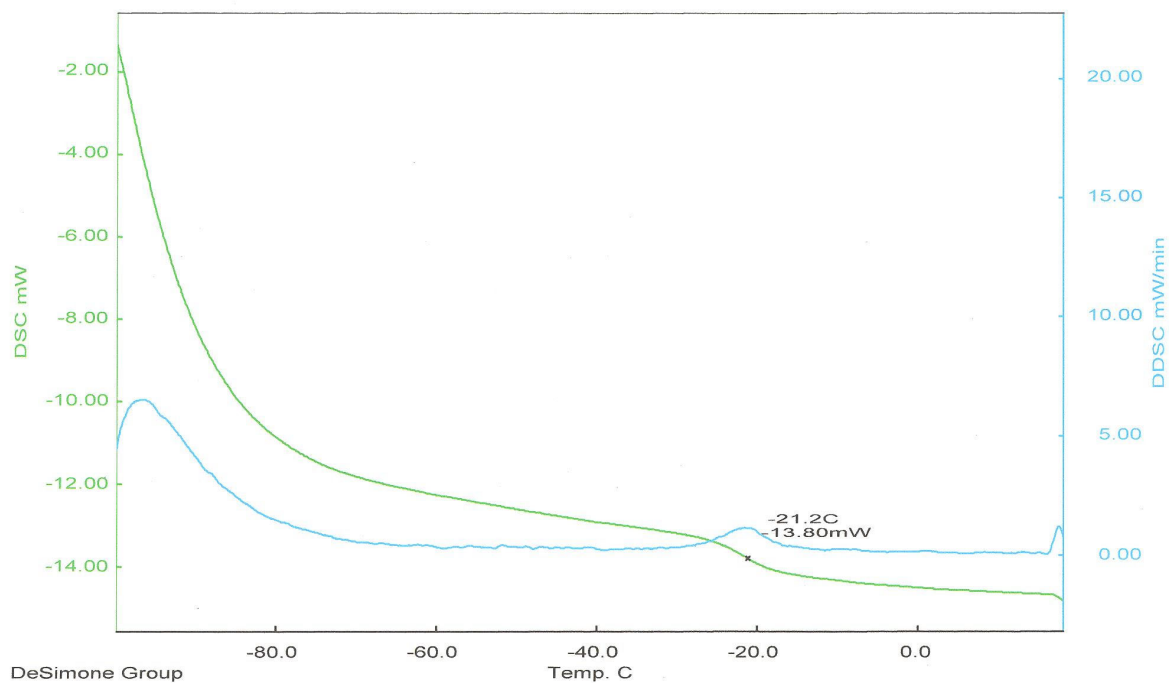
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-100	20	4
2*	-100	25	20	5
3*	25	-100	20	10
4*	-100	25	10	10

Comments:

Operator AHB

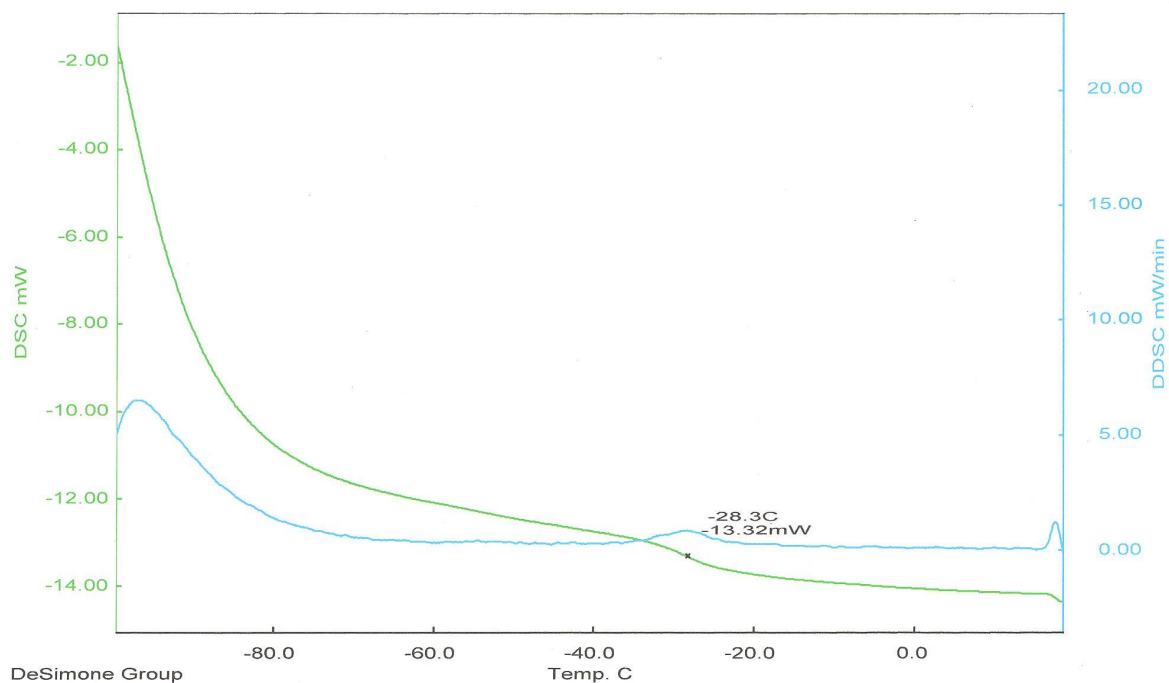
DMDA:DEADA:OD in 0.8:0.2:1.0



DSC of 70 : 30 Copolymer

<< DSC >>

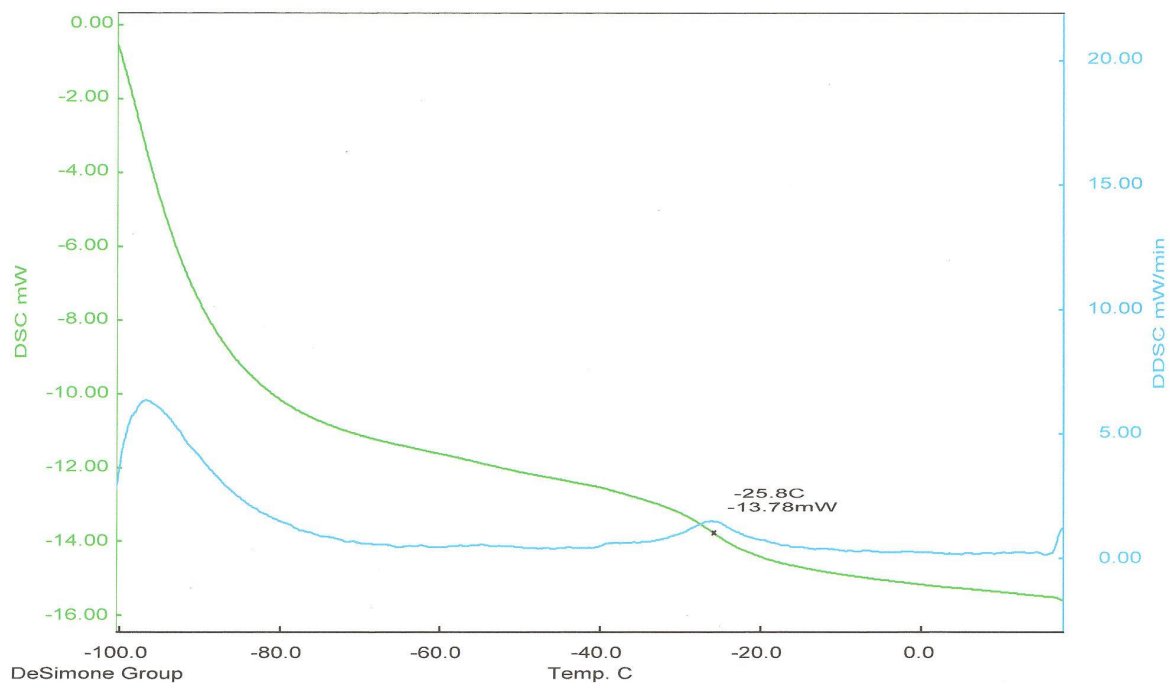
Data Name: AB2-19A	Temperature Program:	Comments:
Date: 5/12/13 12:35	[C] [C/min] [min] [sec]	Operator AHB
Sample: AB2-19A	1* 25 - -100 20 4 0.5	DMDA:DEADA:OD in 0.7:0.3:1.0
	2* -100- 25 20 5 0.5	
	3* 25 - -100 20 10 0.5	
Reference: aluminum reference	4* -100- 25 10 10 0.5	
0 mg		



DSC of 60 : 40 Copolymer

<< DSC >>

Data Name: AB2-23A2	Temperature Program:	Comments:
Date: 6/ 1/26 10:52	[C] [C/min] [min] [sec]	Operator: Olson
Sample: AB2-23A	1* 25 - -100 20 10 0.5	40% DEADA:DMDA:OD copolyester
	2* -100- 25 10 10 0.5	
	3* 25 - -100 20 10 0.5	
Reference: aluminum reference	4* -100- 25 10 1 0.5	
0 mg	5* 25 - 25 40 1 0.5	



DSC of 50 : 50 Copolymer

<< DSC >>

Data Name: AB2-28A

Date: 5/12/13 13:52

Sample: AB2-28A

Reference: aluminum reference

0 mg

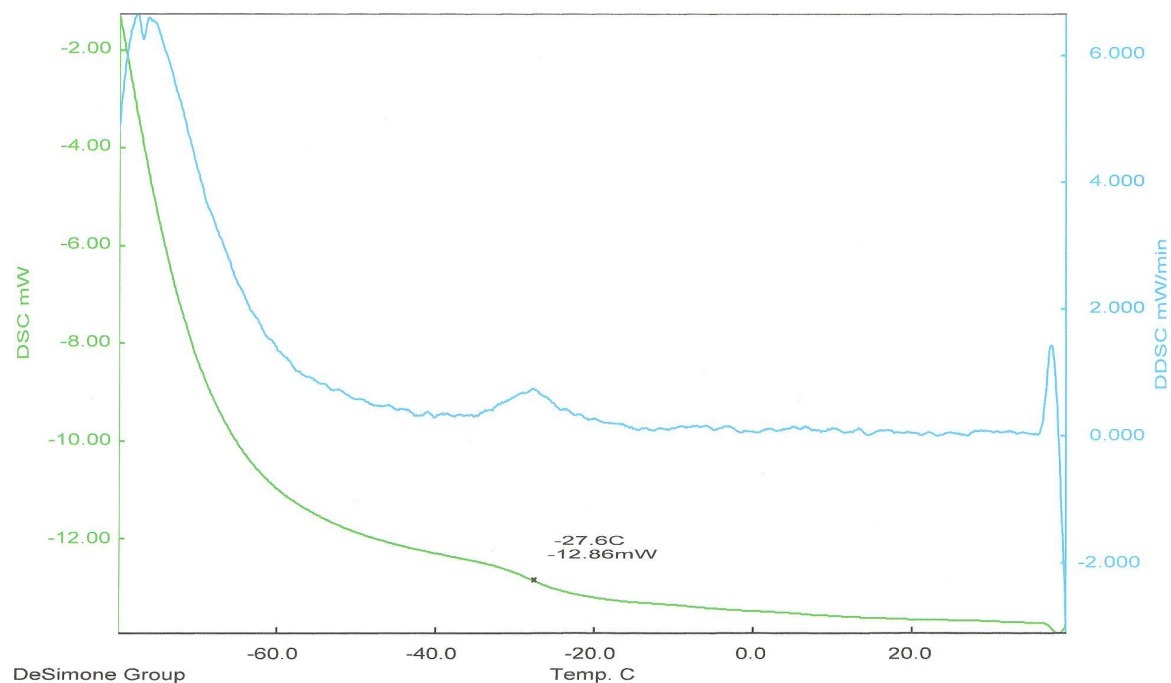
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-80	20	5
2*	-80	-45	20	5
3*	45	-80	20	10
4*	-80	-45	10	10

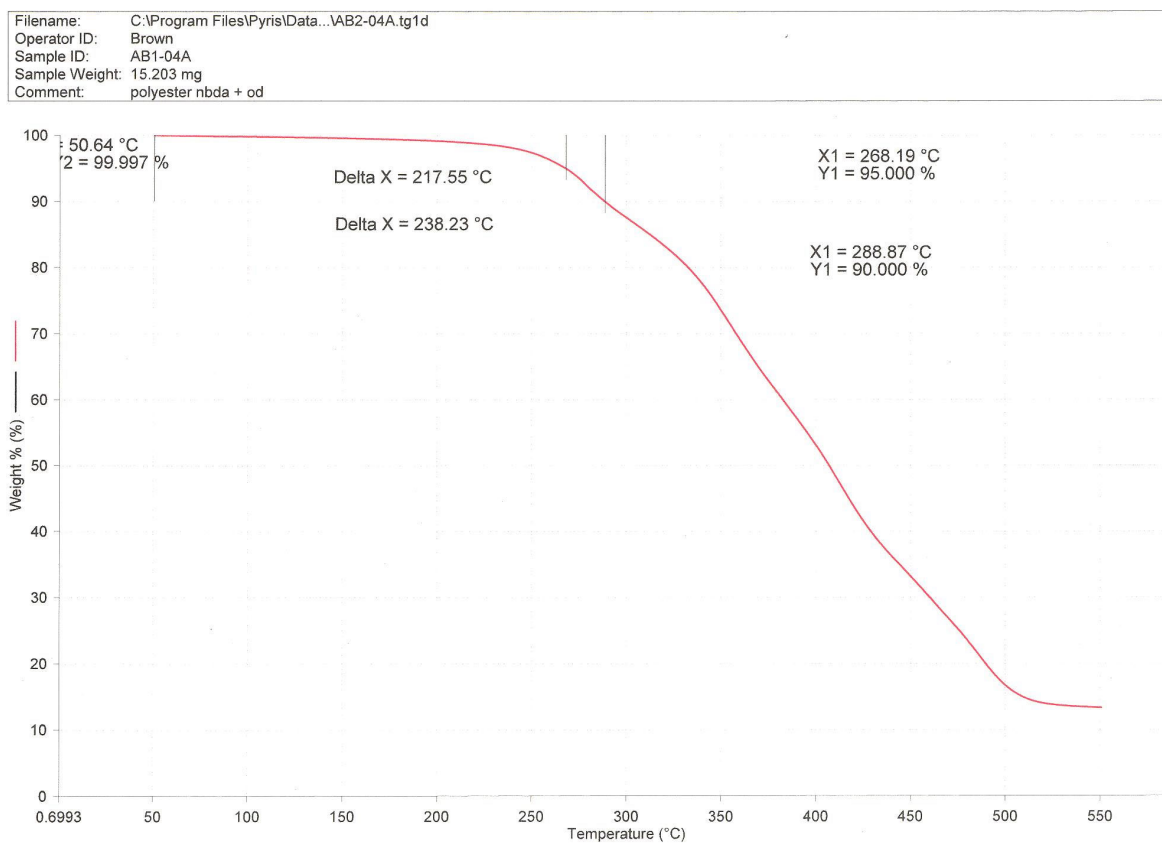
Comments:

Operator AHB

DMDA:DEADA:OD in 0.5:0.5:1.0

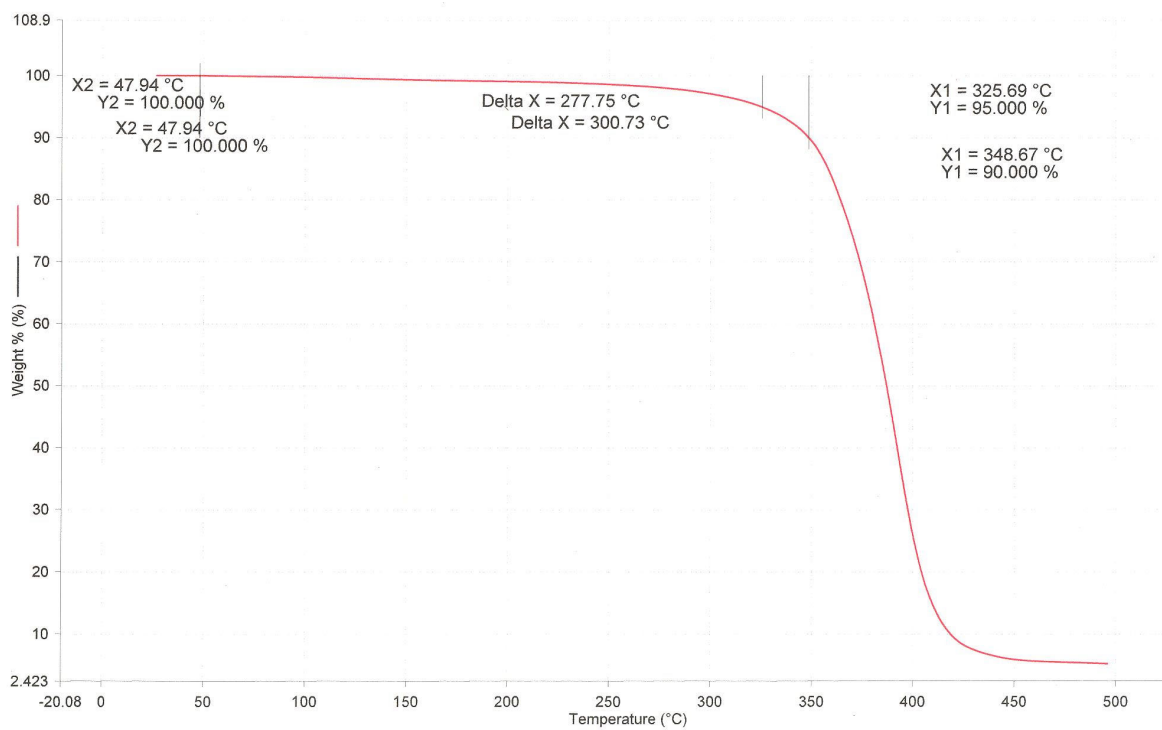


TGA of Polymer 1

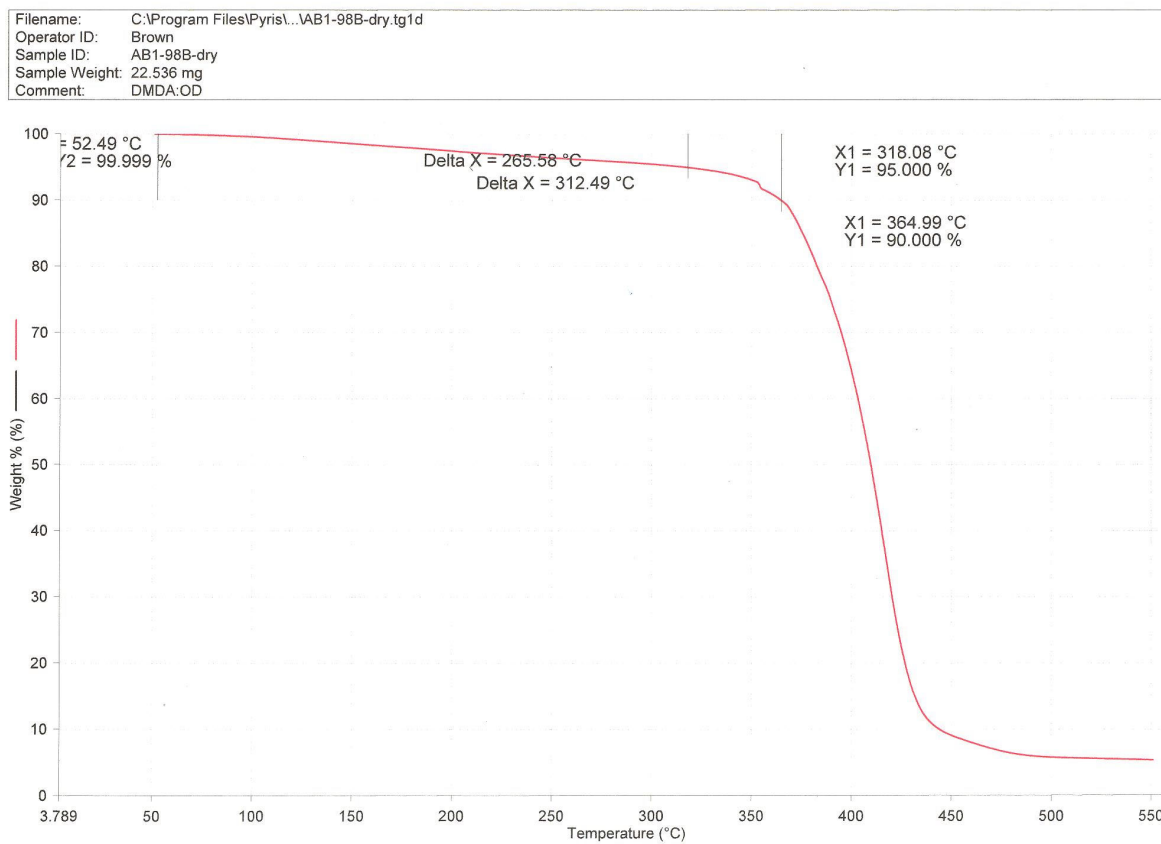


TGA of Polymer 2

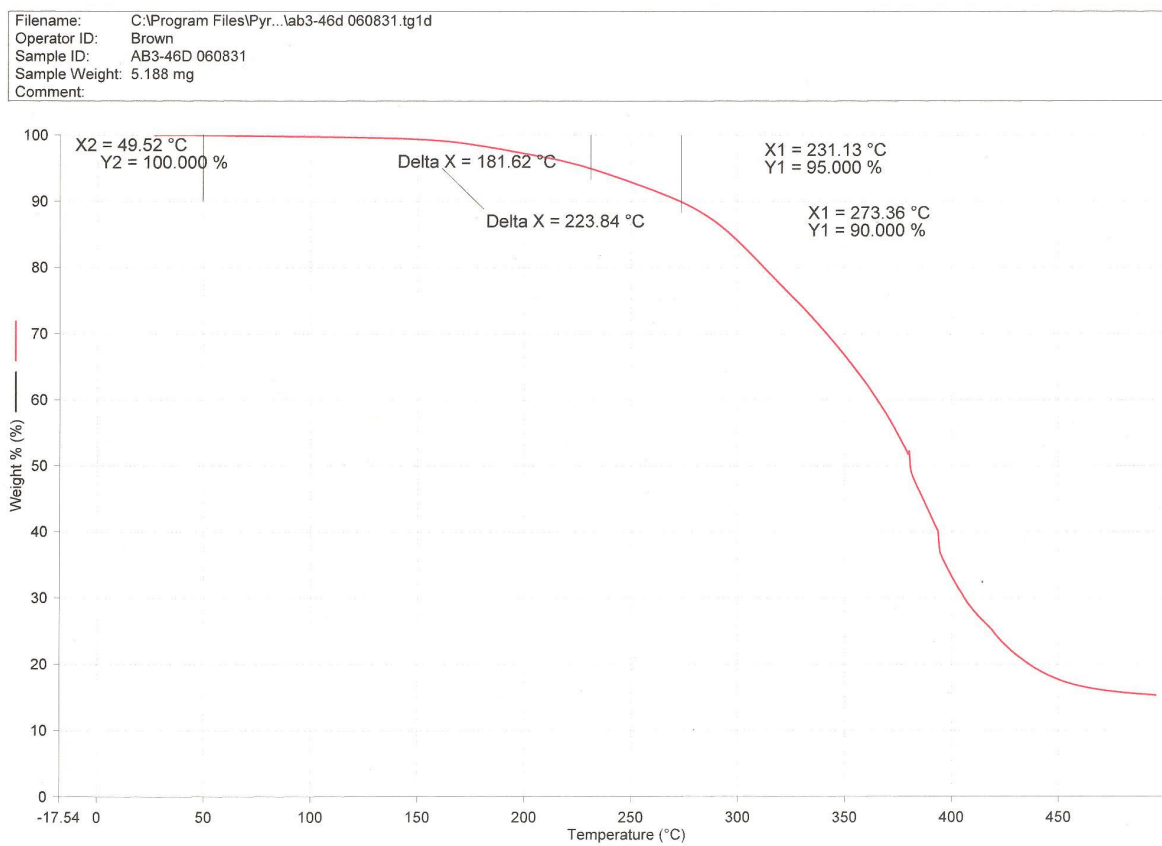
Filename: C:\Program Files\Pyris\Data...\lab3-63b.tg1d
Operator ID: brown
Sample ID: ab3-63b
Sample Weight: 10.359 mg
Comment:



TGA of Polymer 3

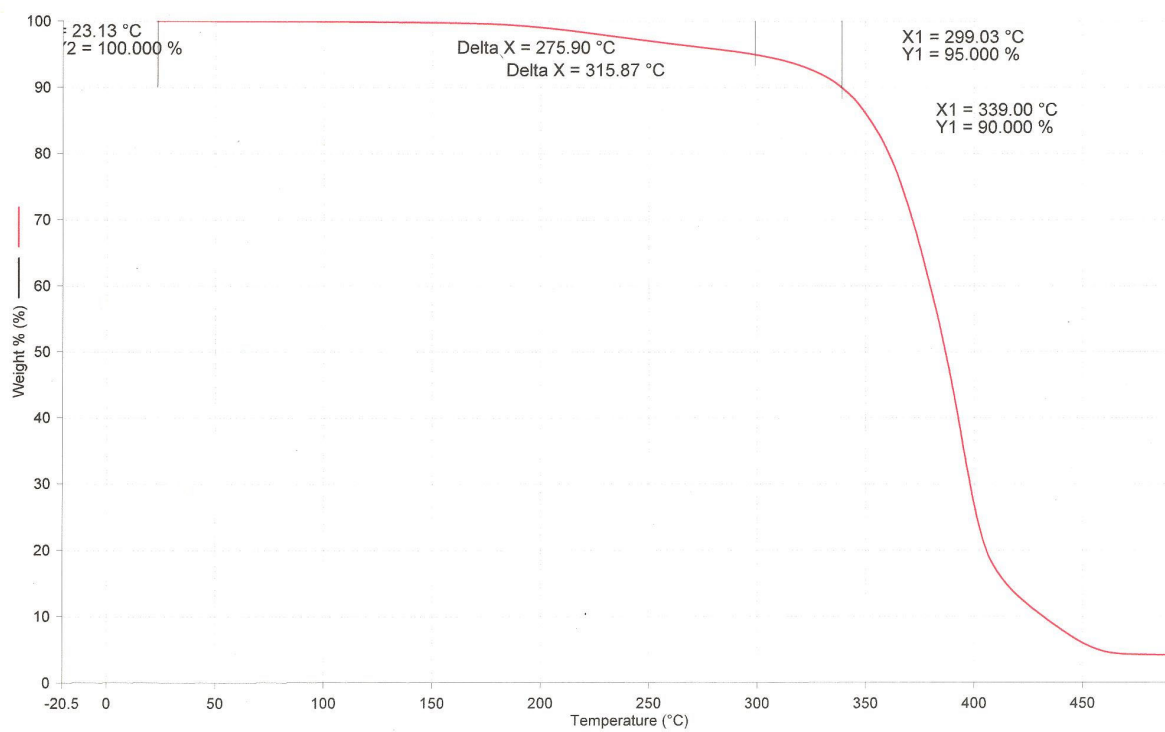


TGA of Polymer 4



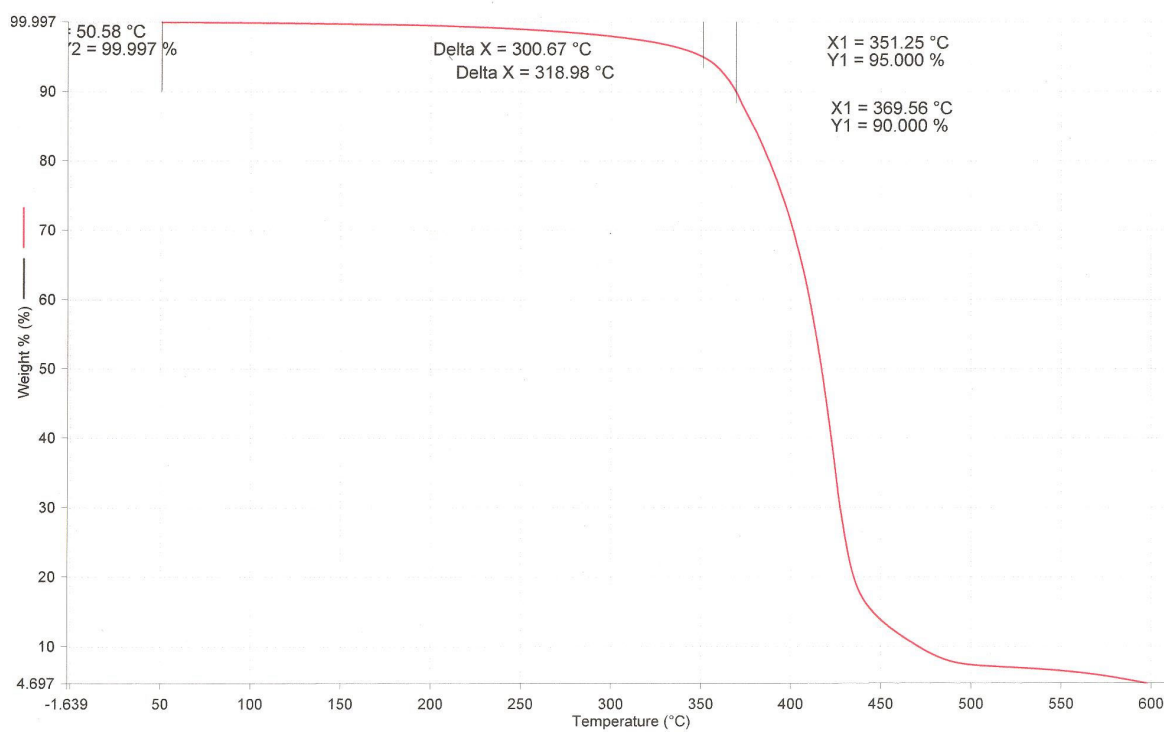
TGA of Polymer 5

Filename: C:\Program Files\Pyr...\AB3-09B_060908.tg1d
Operator ID: andy
Sample ID: Polymer 5
Sample Weight: 14.157 mg
Comment:

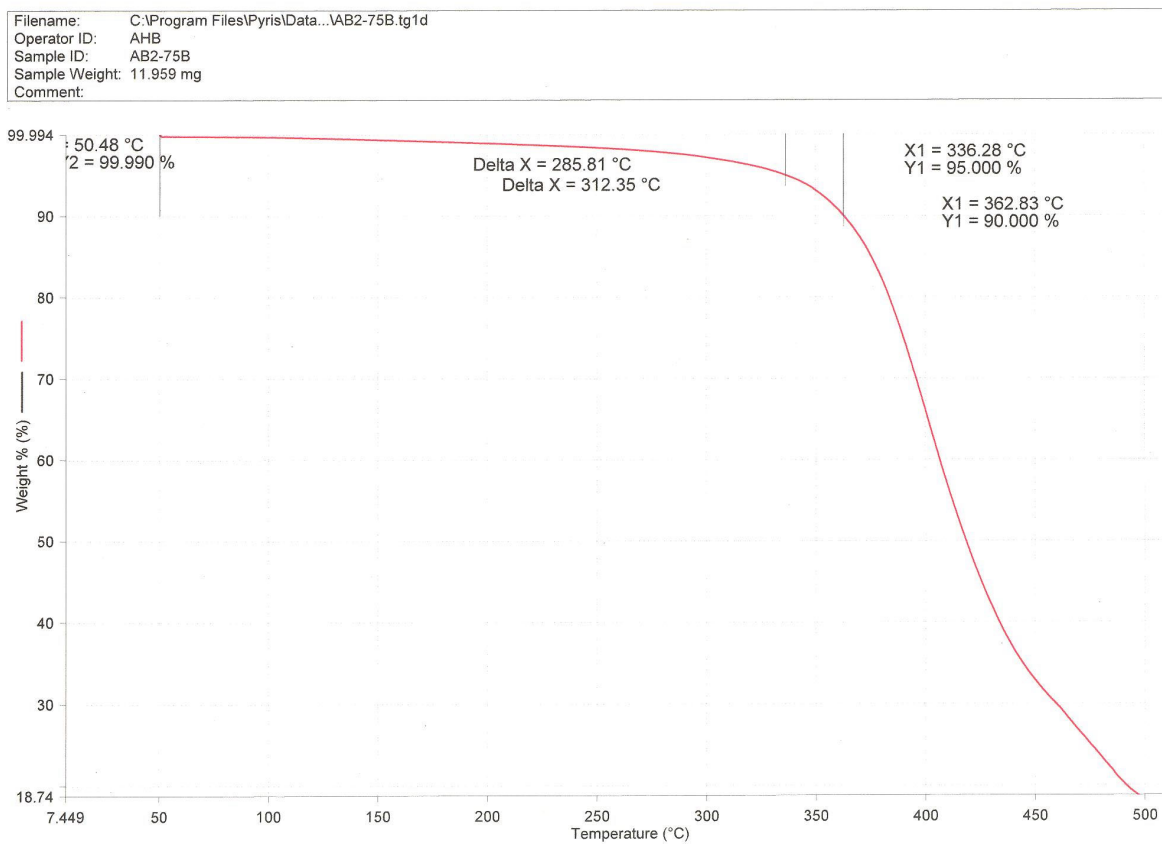


TGA of Polymer 6

Filename: C:\Program Files\Pyris\Data...AB2-55B.tg1d
Operator ID: Brown
Sample ID: AB2-55B
Sample Weight: 21.923 mg
Comment:



TGA of Polymer 7

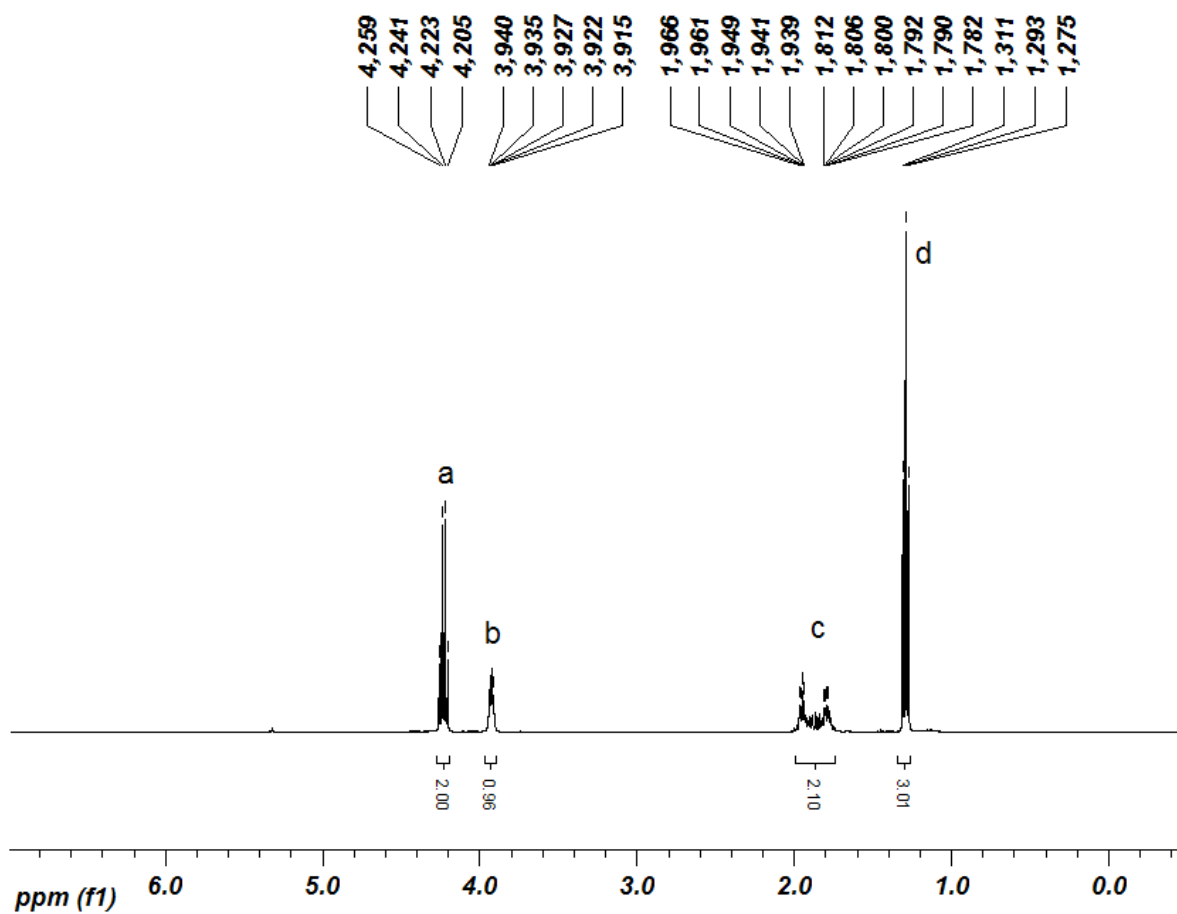


Appendix B

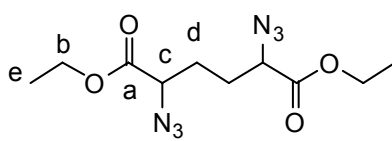
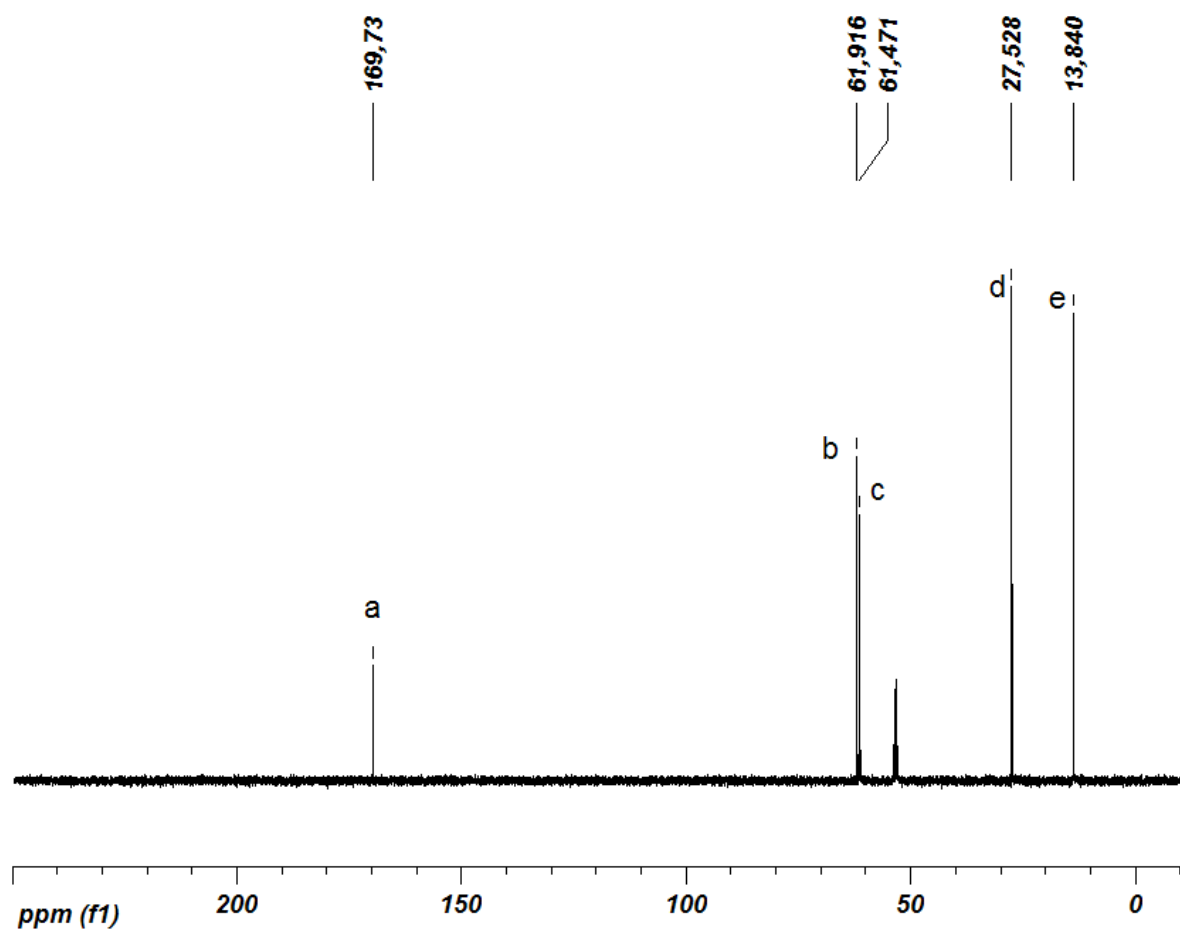
SUPPLEMENTAL MATERIALS FOR CHAPTER 3

Representative ^1H and ^{13}C NMR spectra with assignments

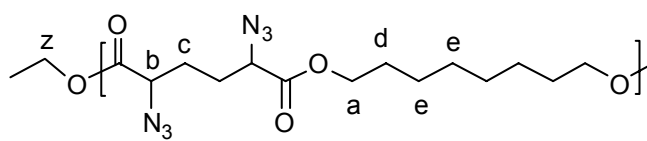
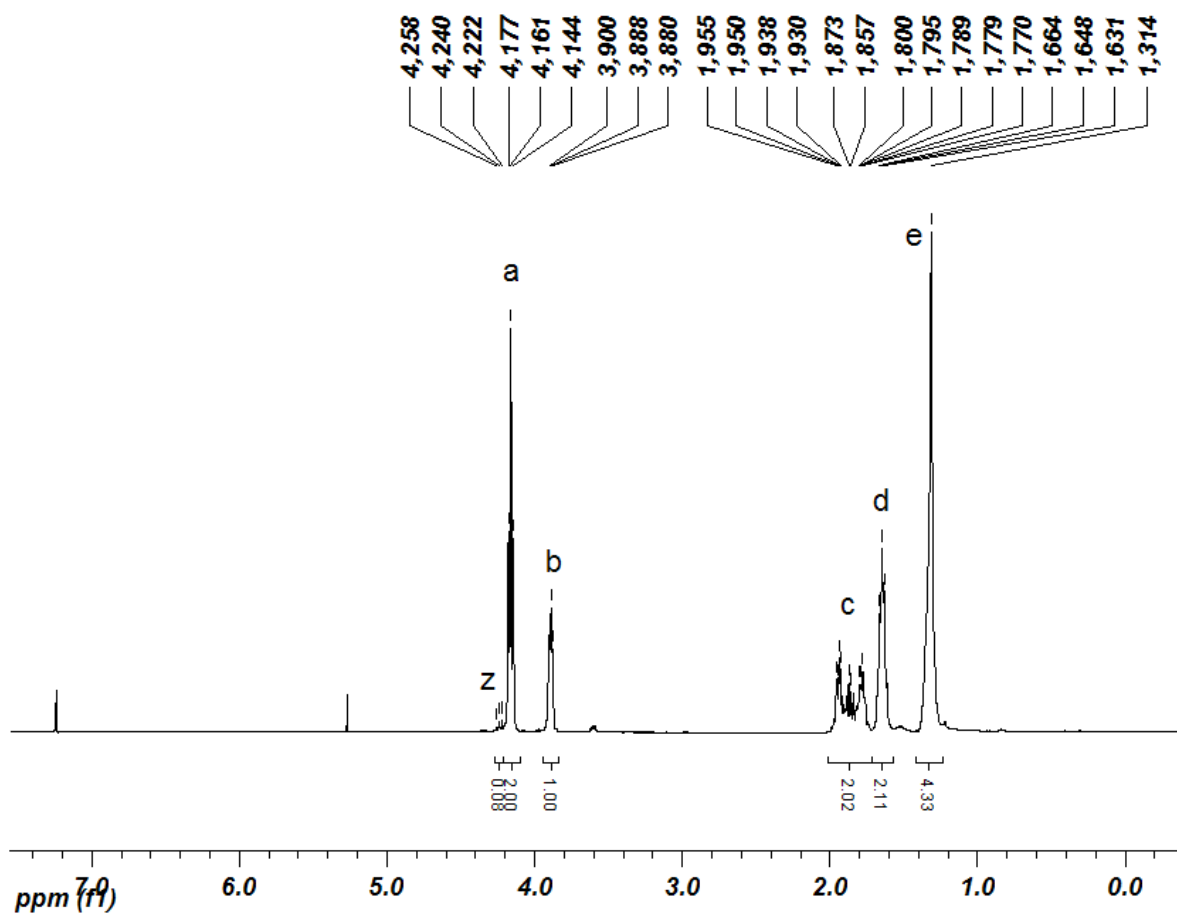
Diethyl 2,5-diazidoadipate (N_3A) – Proton NMR

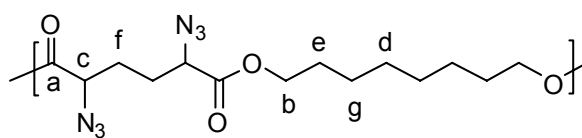
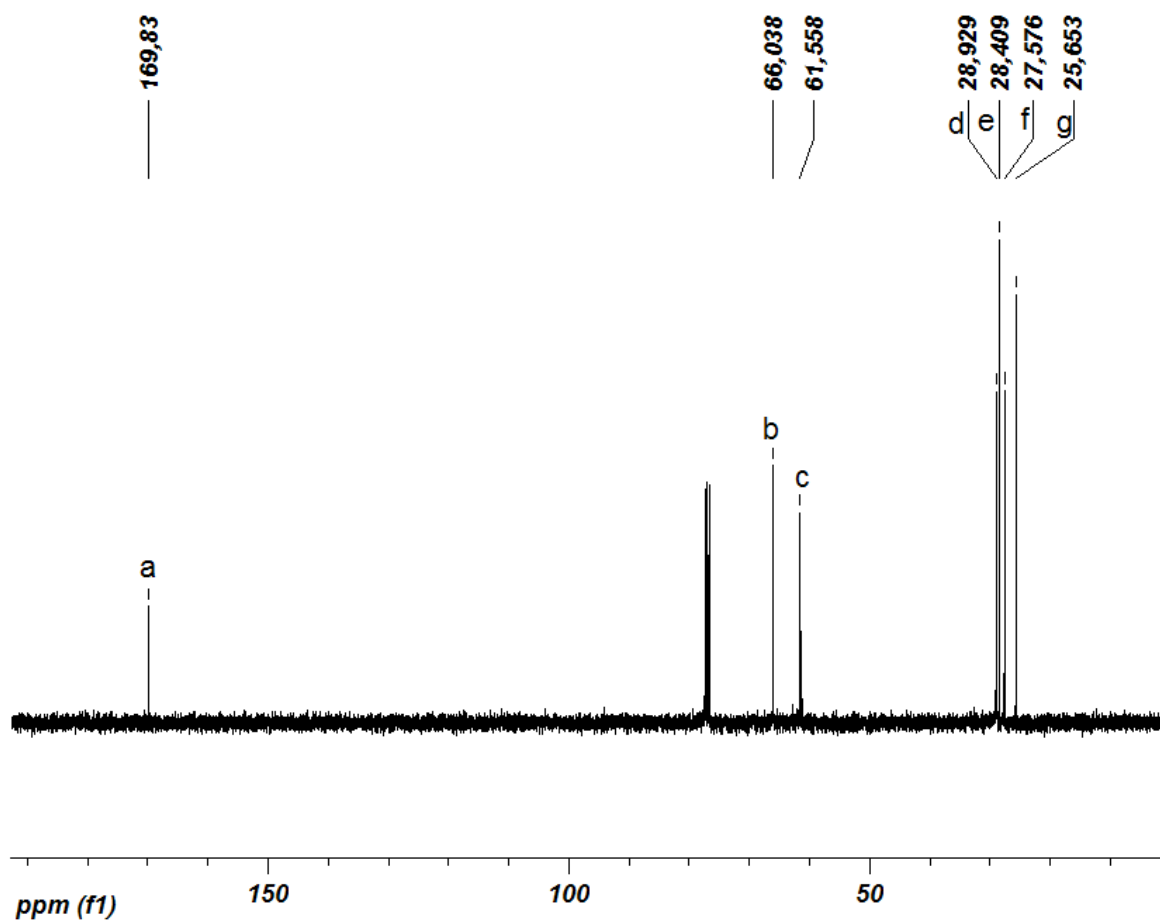


Diethyl 2,5-diazidoadipate (N₃A) – Carbon NMR

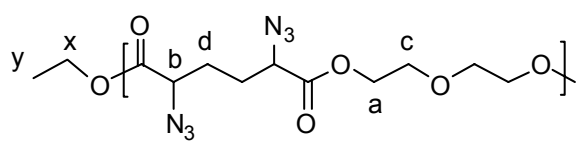
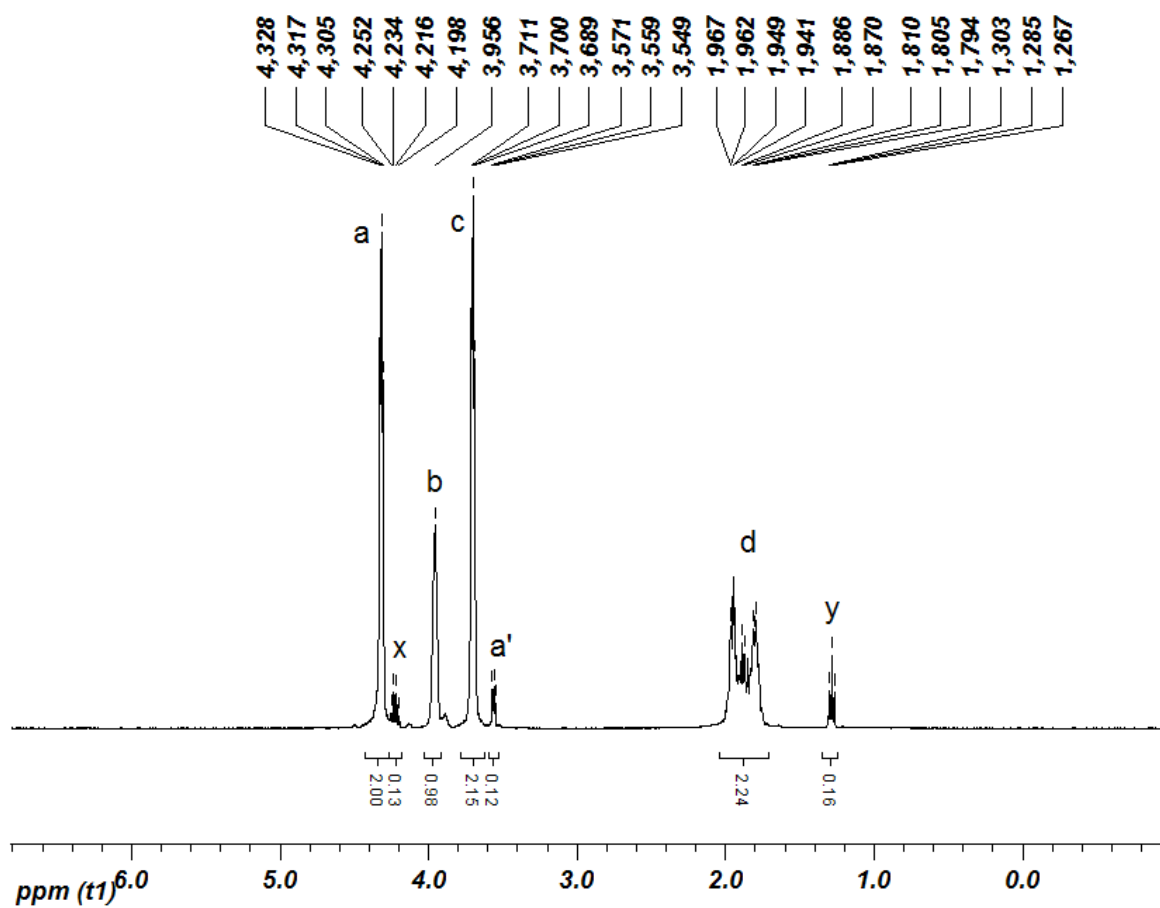


Polyester 1 – Poly(N₃A : OD) – Proton NMR

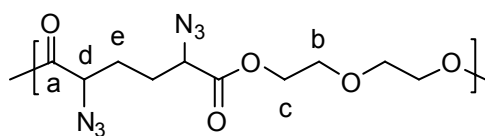
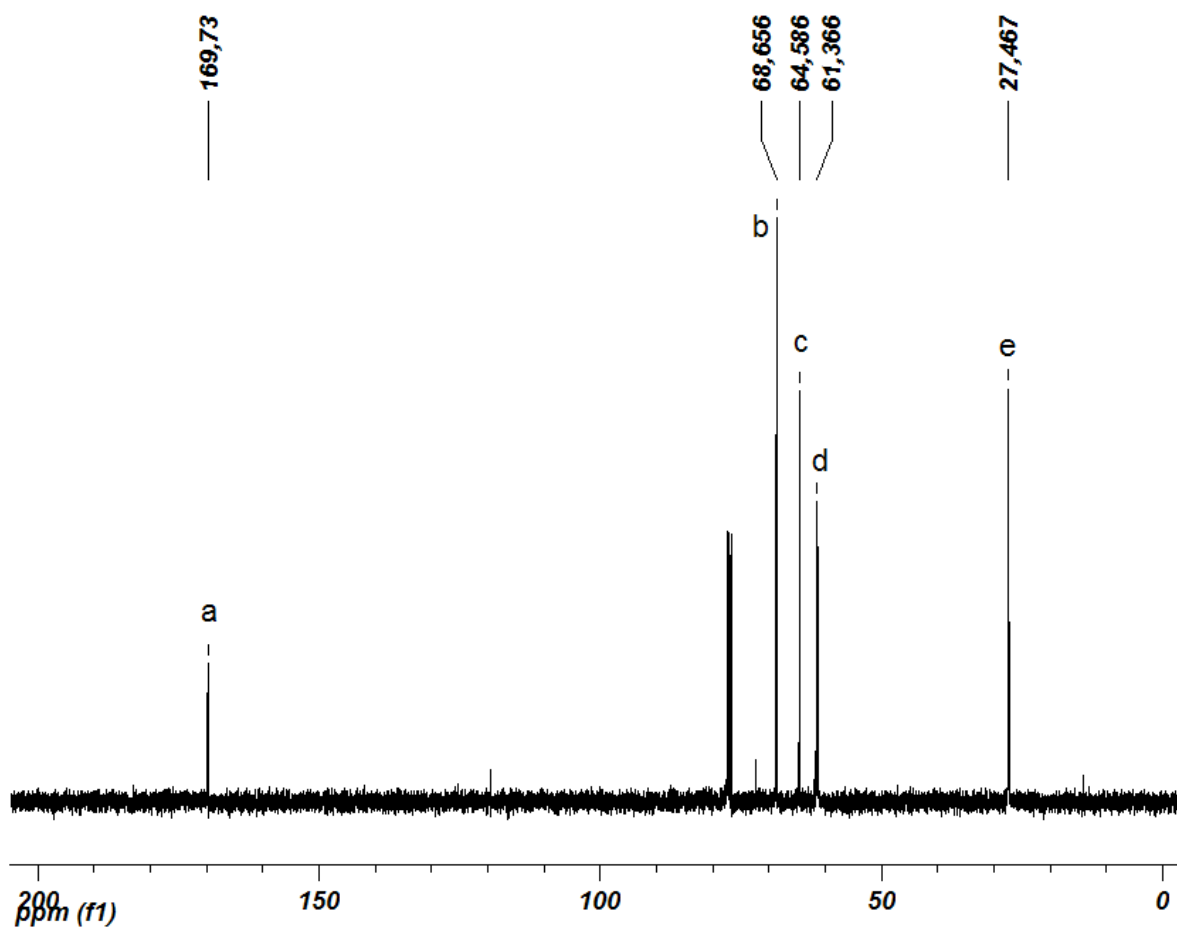


Polyester 1 – Poly(N₃A : OD) – Carbon NMR

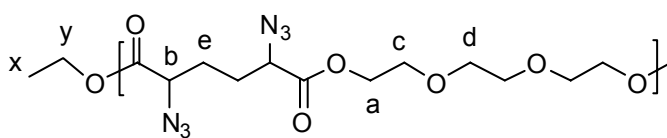
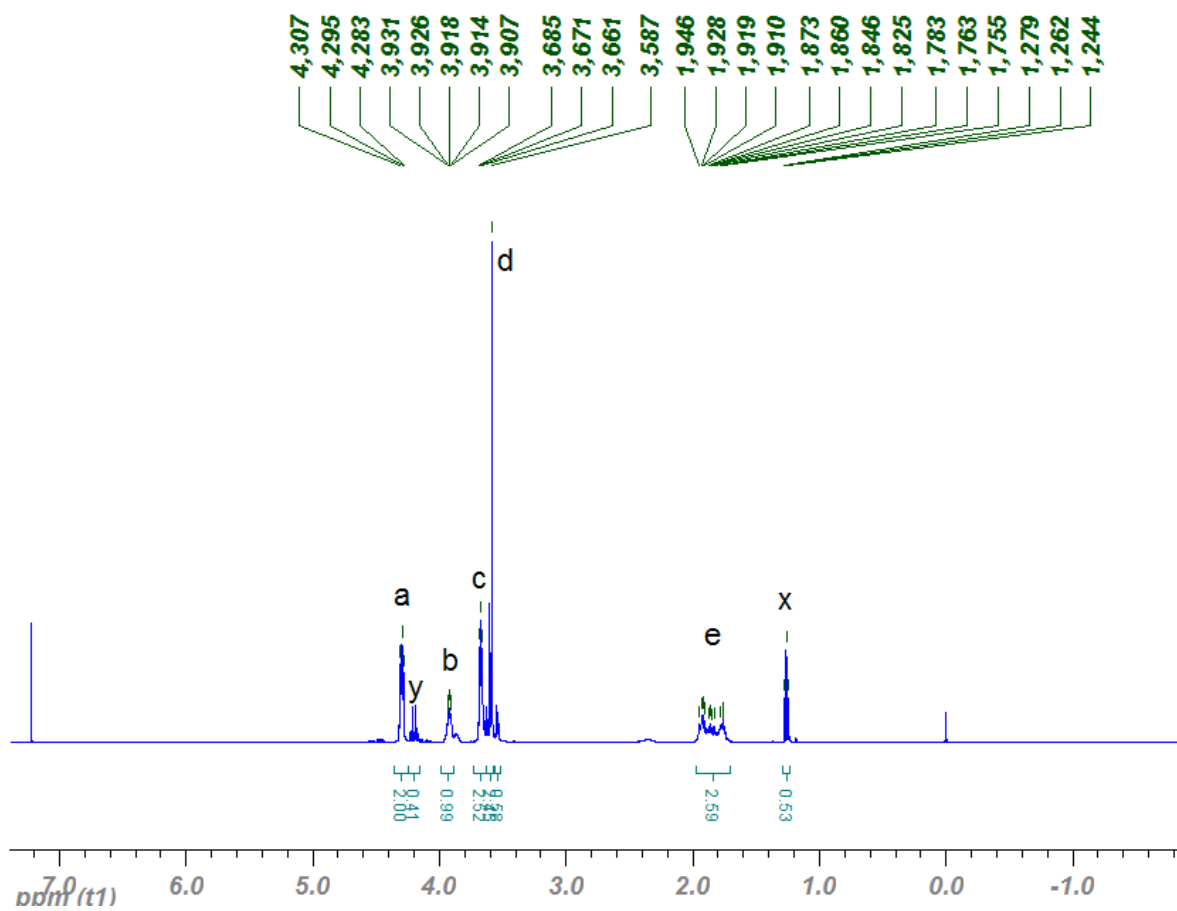
Polyester 2 – Poly(N₃A : 2EG) – Proton NMR



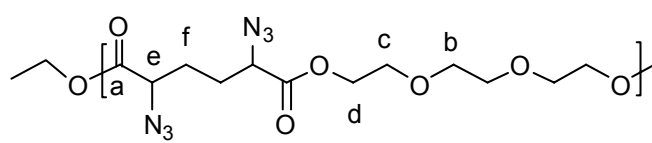
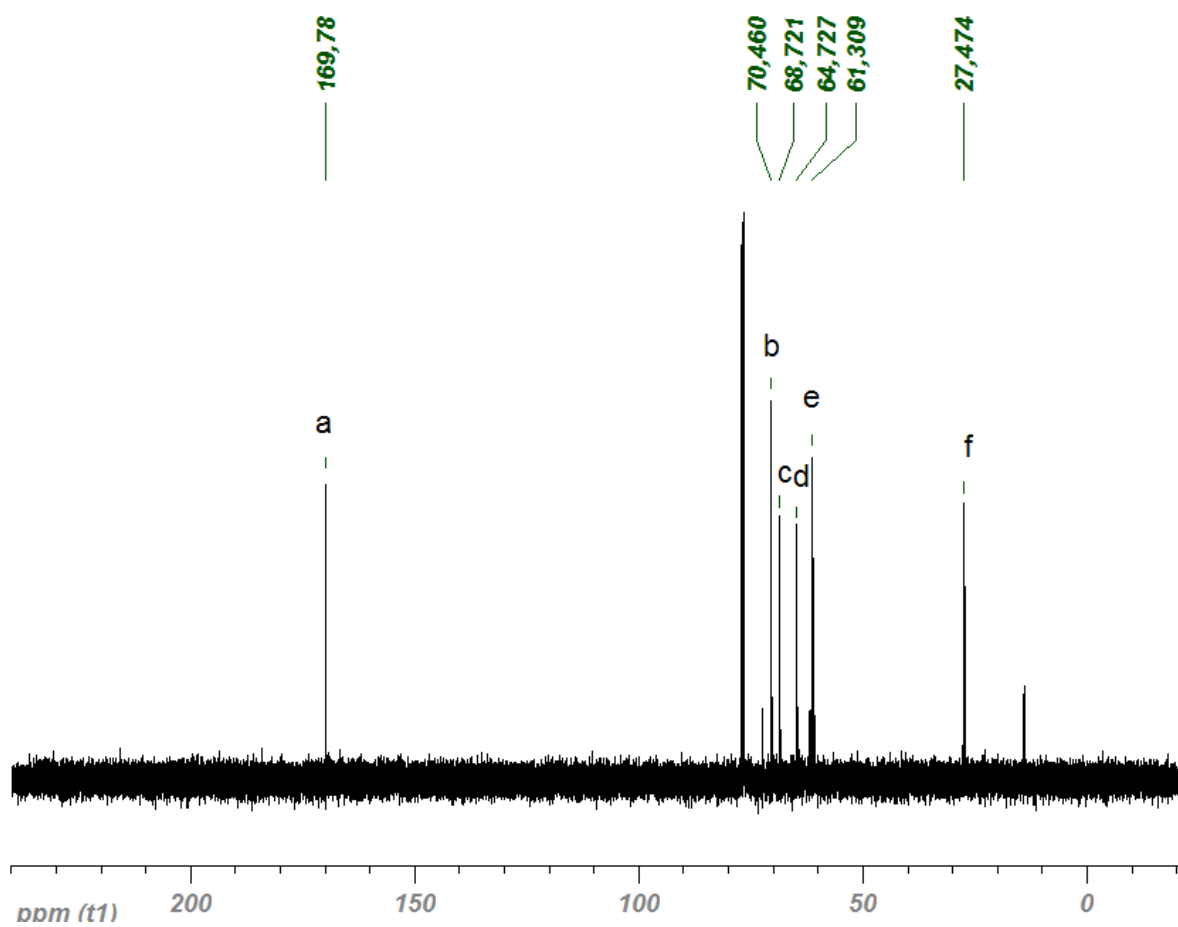
Polyester 2 – Poly(N₃A : 2EG) – Carbon NMR



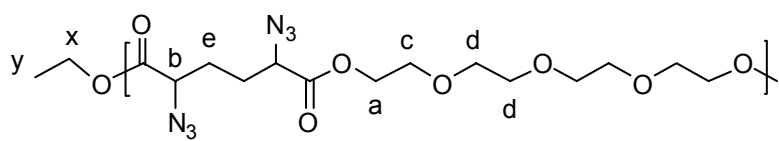
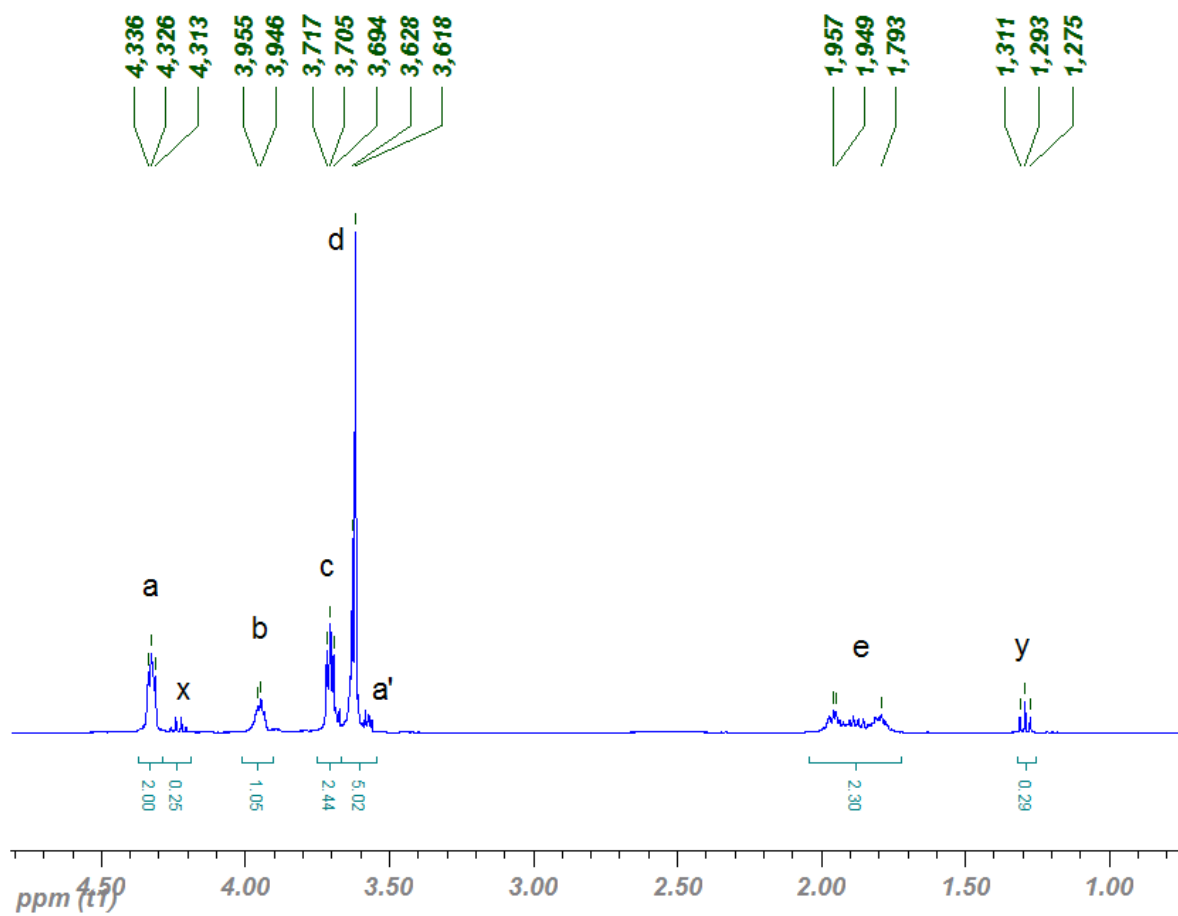
Polyester 3 – Poly(N₃A : 3EG) – Proton NMR



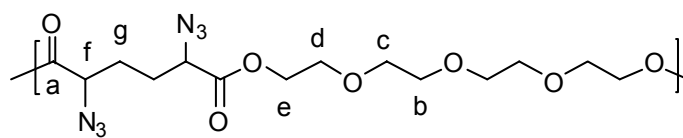
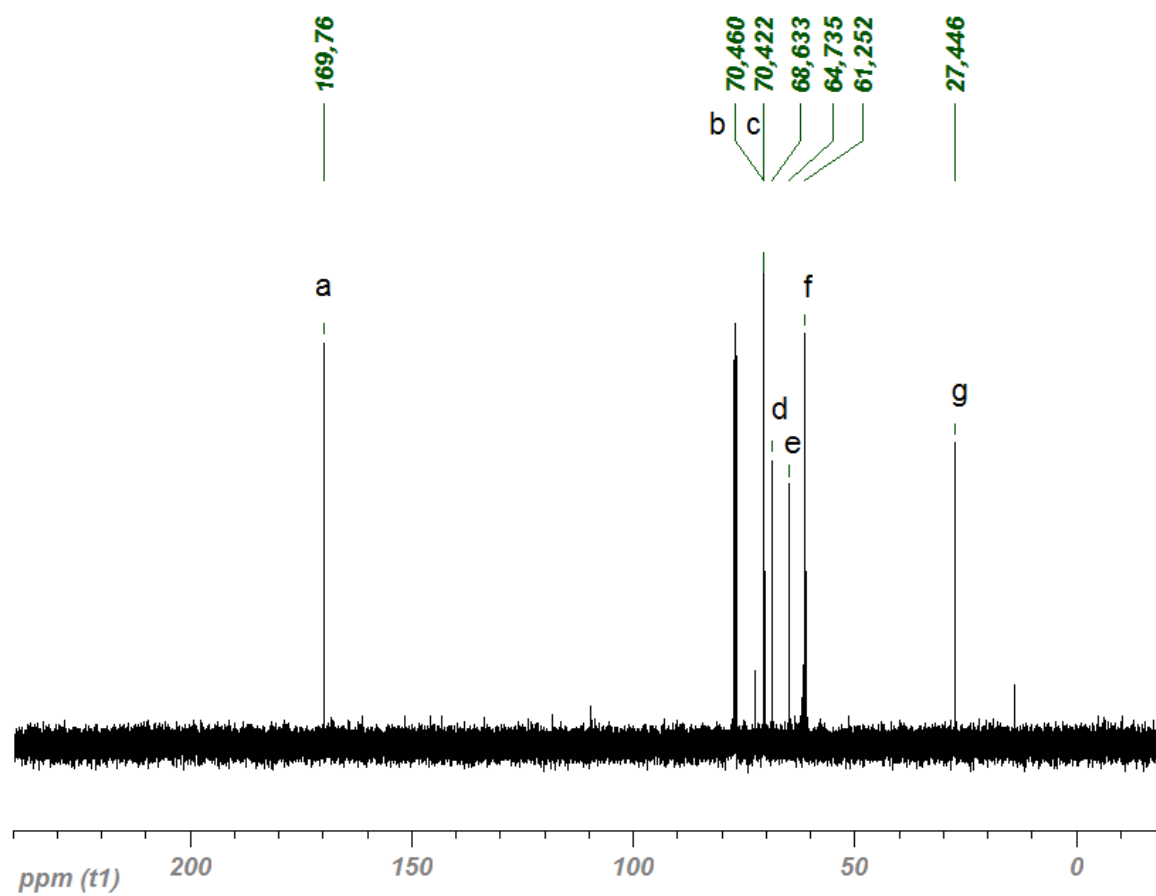
Polyester 3 – Poly(N₃A : 3EG) – Carbon NMR



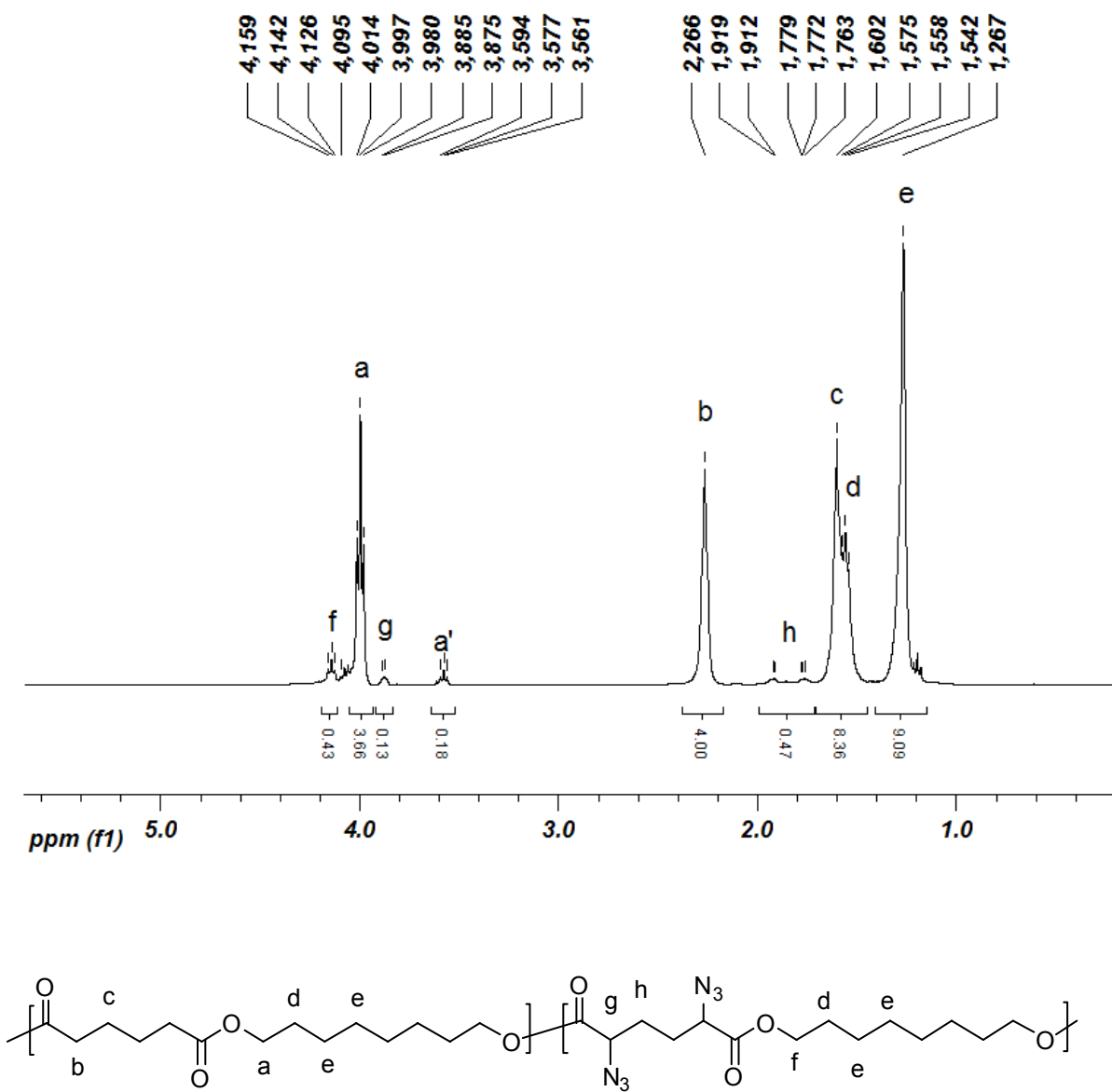
Polyester 4 – Poly(N₃A : 4EG) – Proton NMR



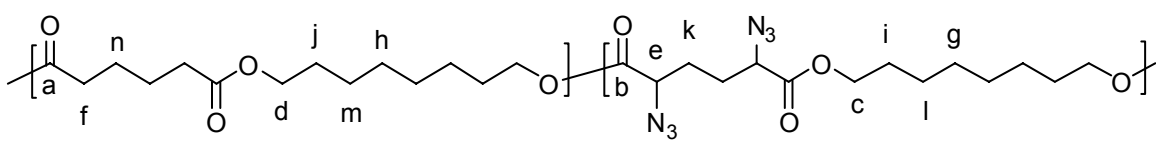
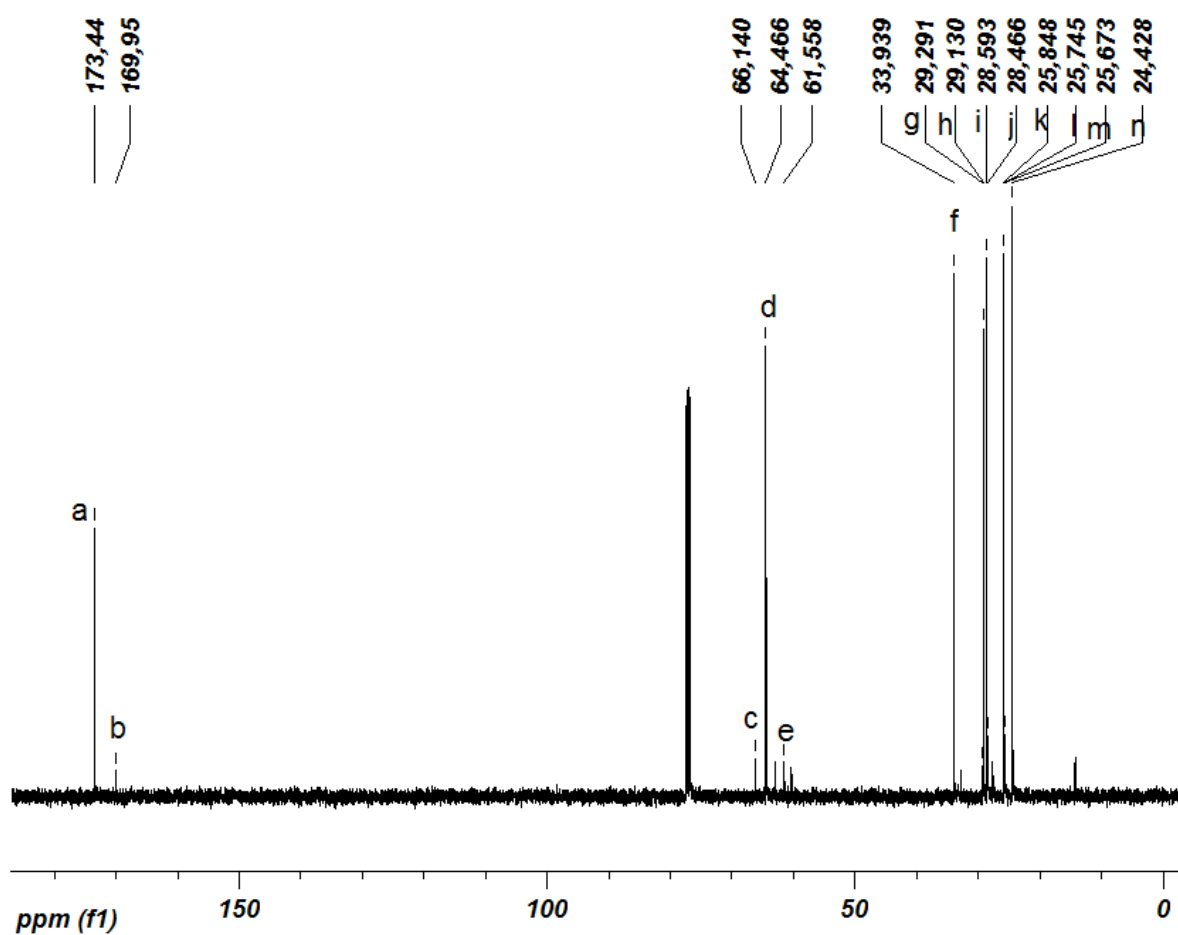
Polyester 4 – Poly(N₃A : 4EG) – Carbon NMR

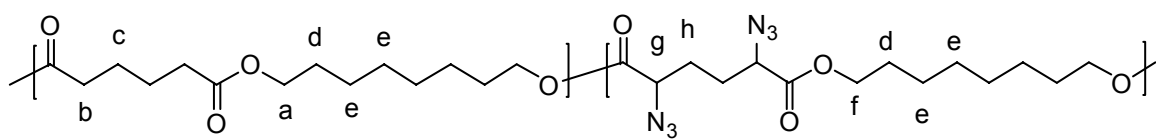
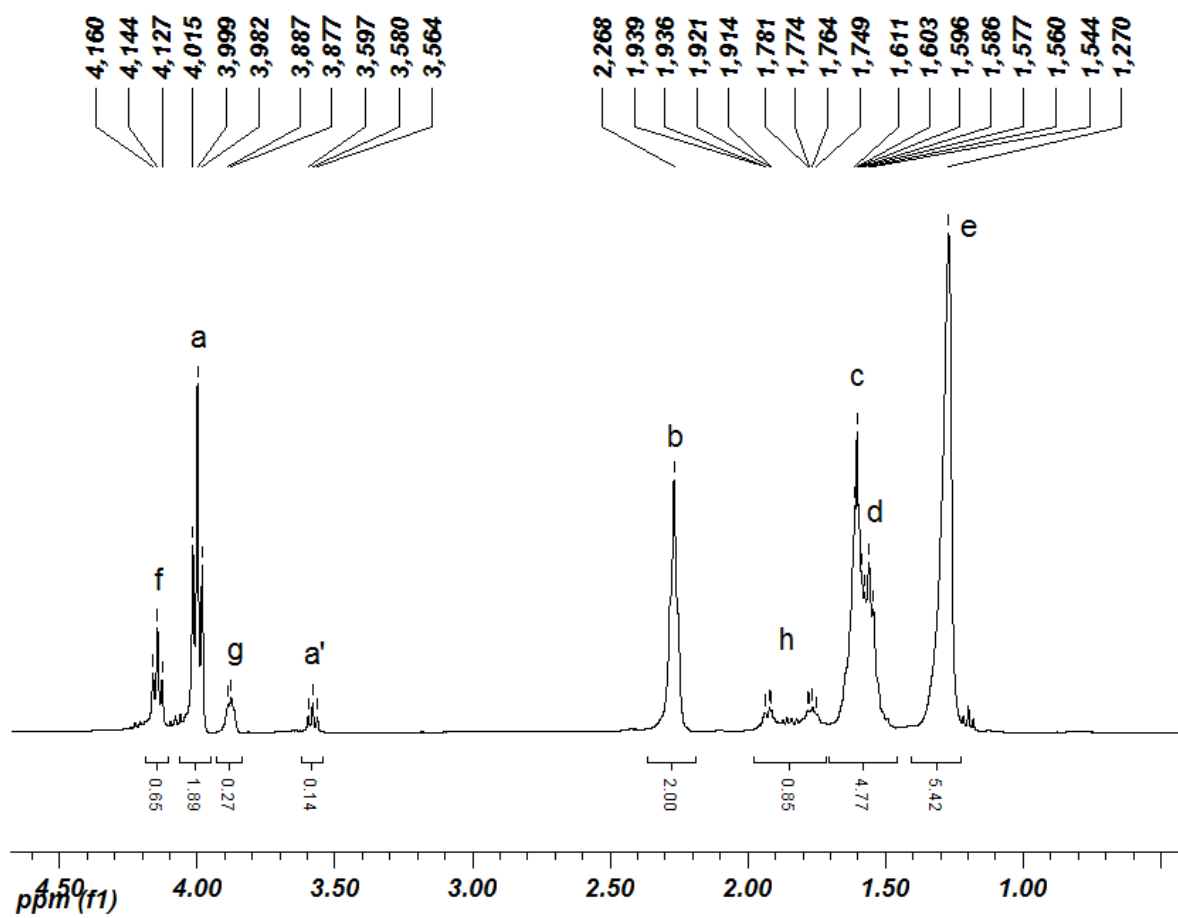


Poly(N₃A : DEA : OD) (10 : 90 : 100) – Proton NMR

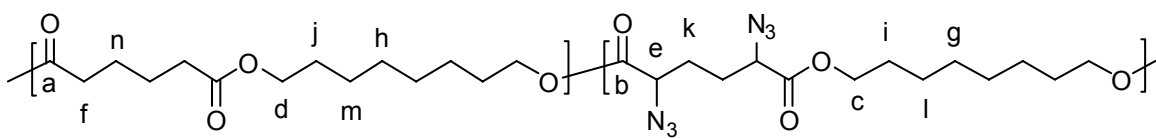
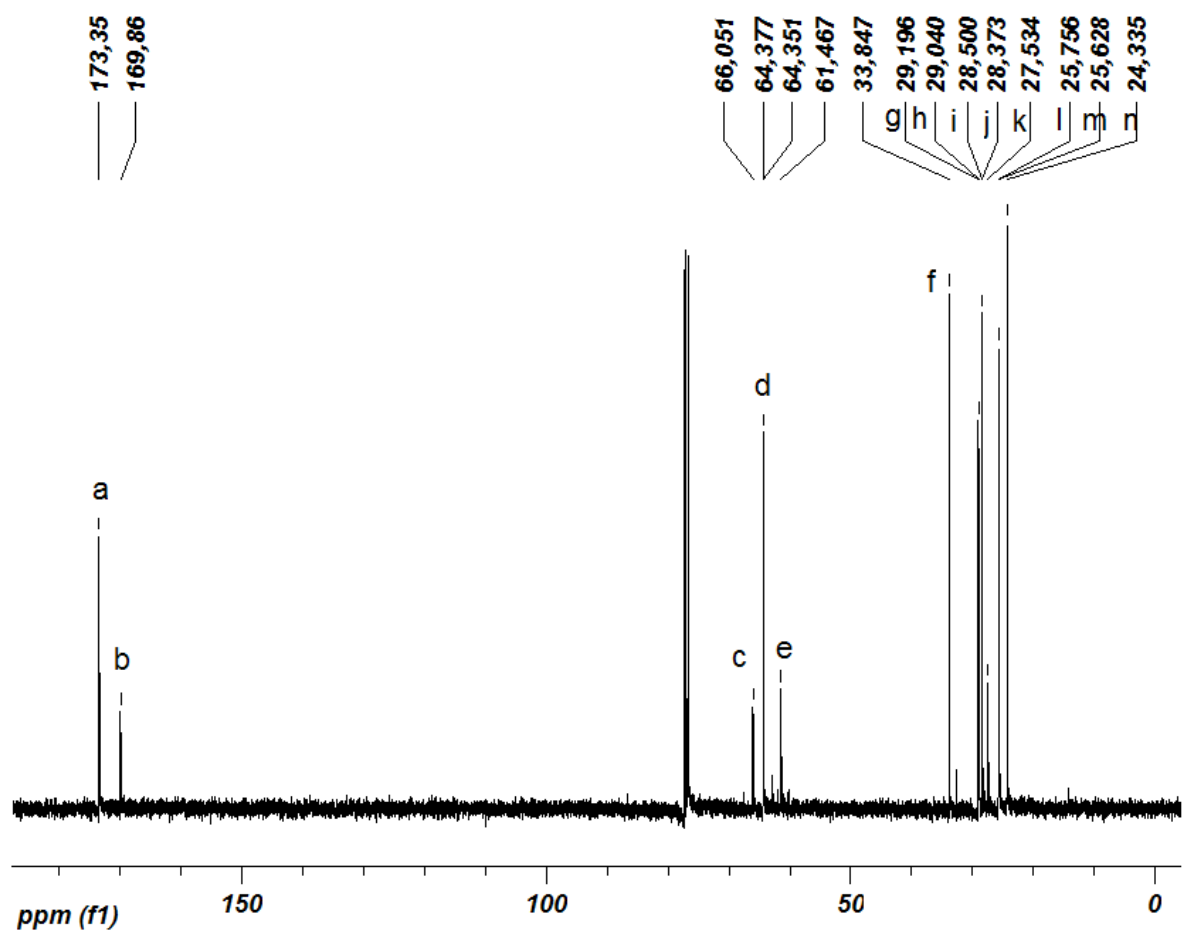


Poly(N₃A : DEA : OD) (10 : 90 : 100) – Carbon NMR

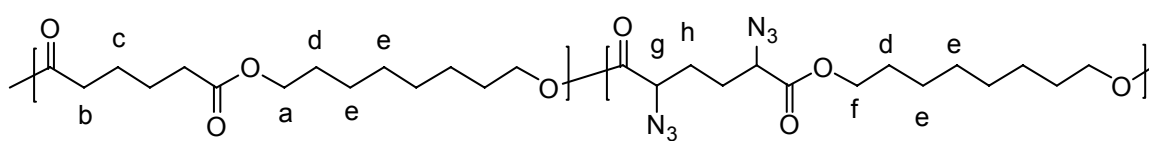
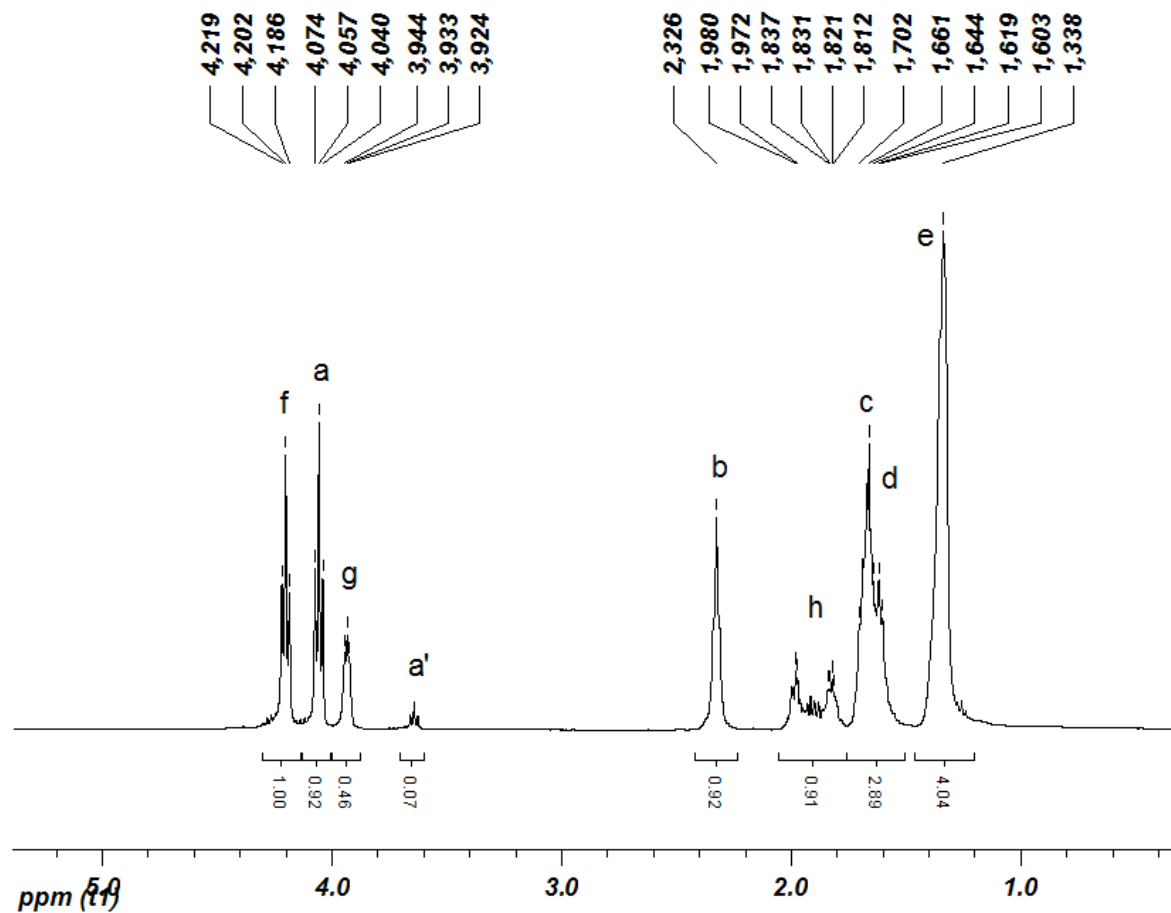


Poly(N₃A : DEA : OD) (25 : 75 : 100) – Proton NMR

Poly(N₃A : DEA : OD) (25 : 75 : 100) – Carbon NMR



Poly(N₃A : DEA : OD) (50 : 50 : 100) – Proton NMR



173,46
169,97

66,166
64,489
61,580

33,955
29,108
29,072
28,606
28,479
27,643
25,864
25,760
24,442

a b

c d e

f

g h i j k l m n

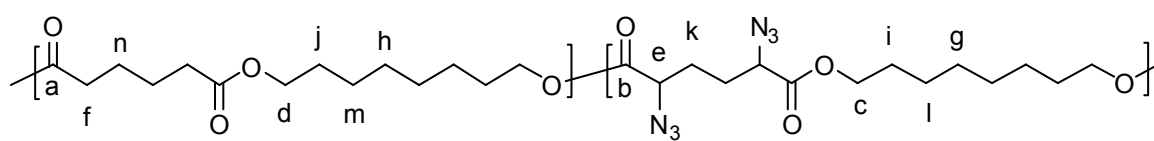
ppm (t1)

150

100

50

0



4.192
4.176
4.159
4.047
4.030
4.013
3.917
3.906
3.897
3.632
3.615
3.599
2.299
1.971
1.966
1.945
1.815
1.811
1.805
1.678
1.662
1.634
1.628
1.617
1.610
1.594
1.329

f
a
g
a'
b
h
c
d
e

1.00
0.33
0.51
0.03
0.34
1.12
1.75
2.83

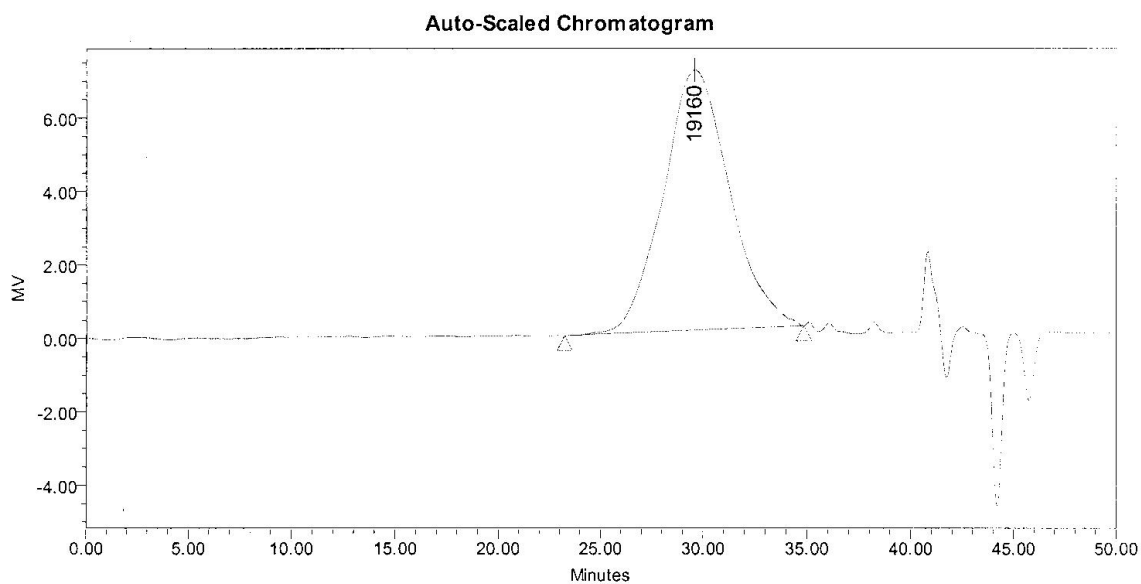
ppm (t1)
5.0
4.0
3.0
2.0
1.0

c
b
a
d
e
g
h
N₃
N₃
d
e
f
e

Representative GPC chromatograms

Polyester 1

SAMPLE INFORMATION			
Sample Name:	ab4-91	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	samples 070515
Vial:	91	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	5/15/2007 4:24:14 PM EDT		
Date Processed:	6/22/2007 10:14:41 AM EDT		

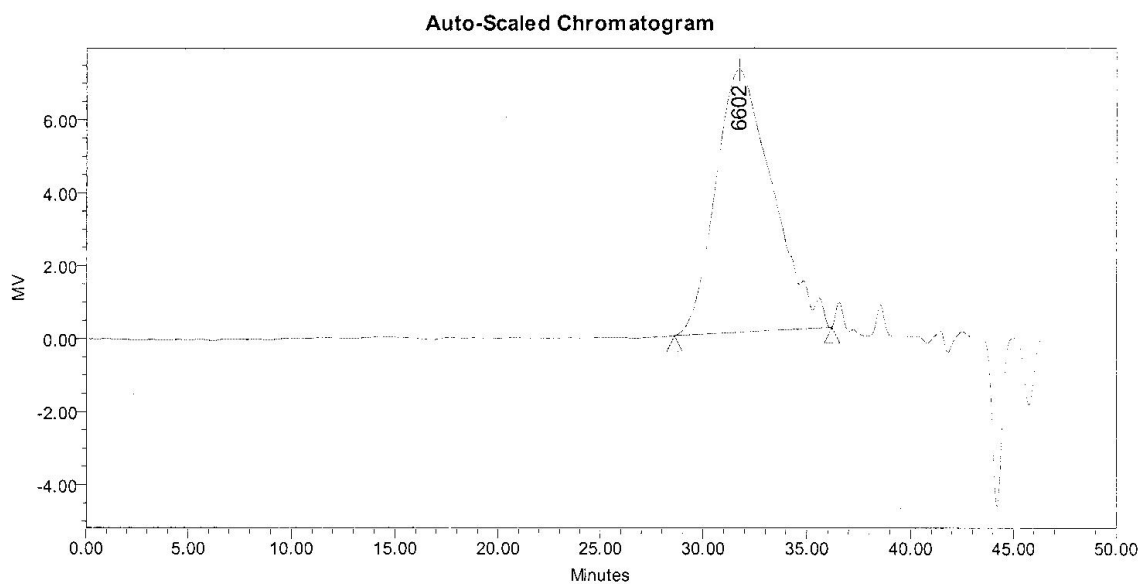


GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Poly dispersity	K	alpha
1		13063	23787		19160	41688	71742	1.820905		

Polyester 2 GPC

SAMPLE INFORMATION			
Sample Name:	AB4-98	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	SAMPLES 070521
Vial:	93	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	5/21/2007 11:50:08 PM EDT		
Date Processed:	5/22/2007 7:36:09 AM EDT		

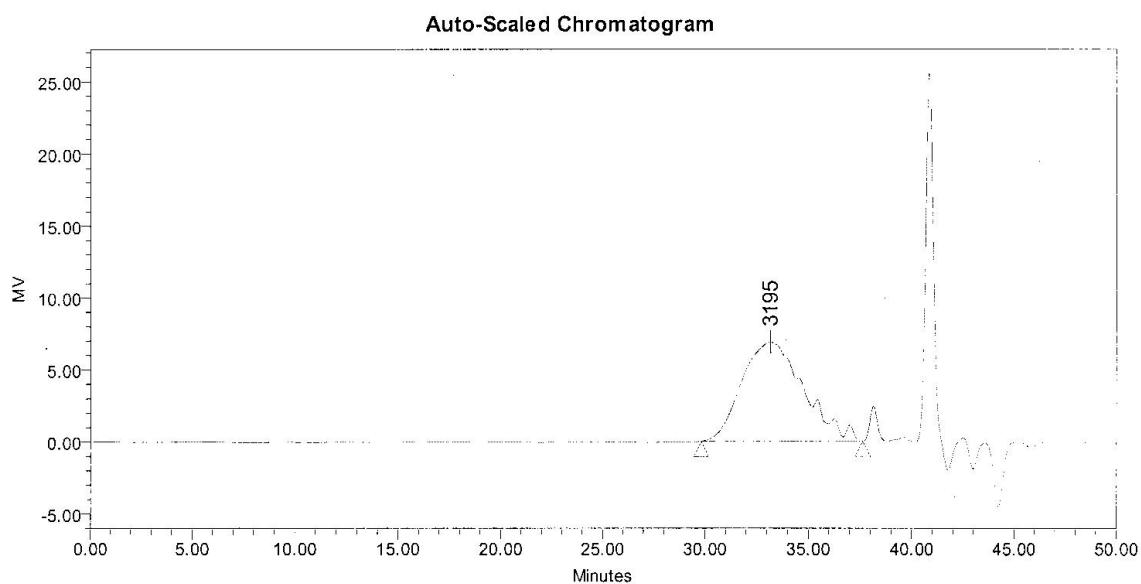


GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Poly dispersity	K	alpha
1		4194	6542		6602	9064	11534	1.559819		

Polyester 3 GPC

SAMPLE INFORMATION			
Sample Name:	ab5-10	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	0740612
Vial:	10	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	6/12/2007 11:18:01 AM EDT		
Date Processed:	12/7/2007 11:30:30 AM EST		



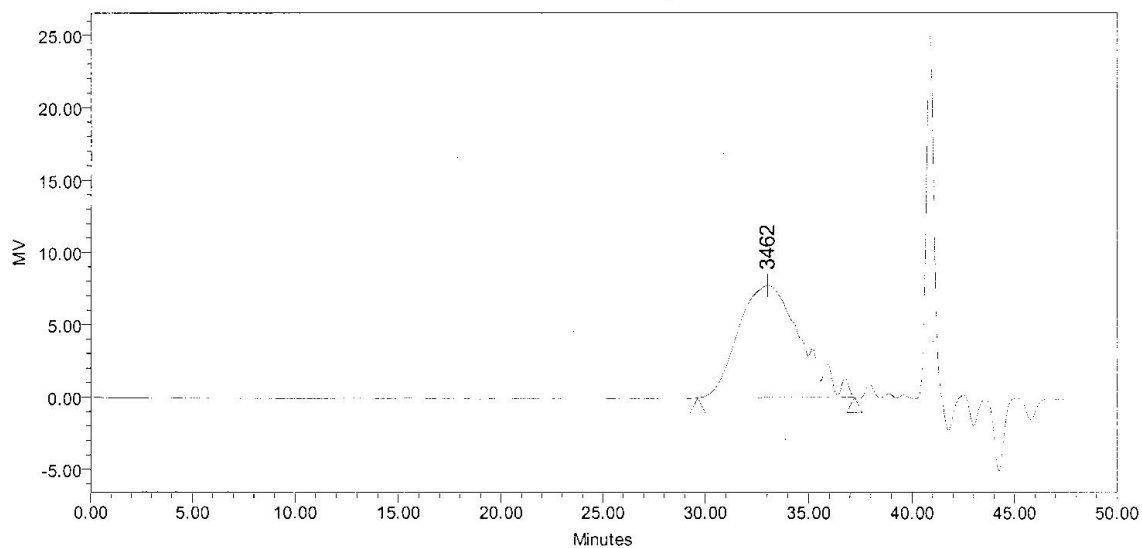
GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Poly dispersity	K	alpha
1		2061	3480		3195	5019	6482	1.688507		

Polyester 4 GPC

SAMPLE INFORMATION			
Sample Name:	ab5-11	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	0740612
Vial:	11	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	6/12/2007 12:09:27 PM EDT		
Date Processed:	12/7/2007 11:30:35 AM EST		

Auto-Scaled Chromatogram

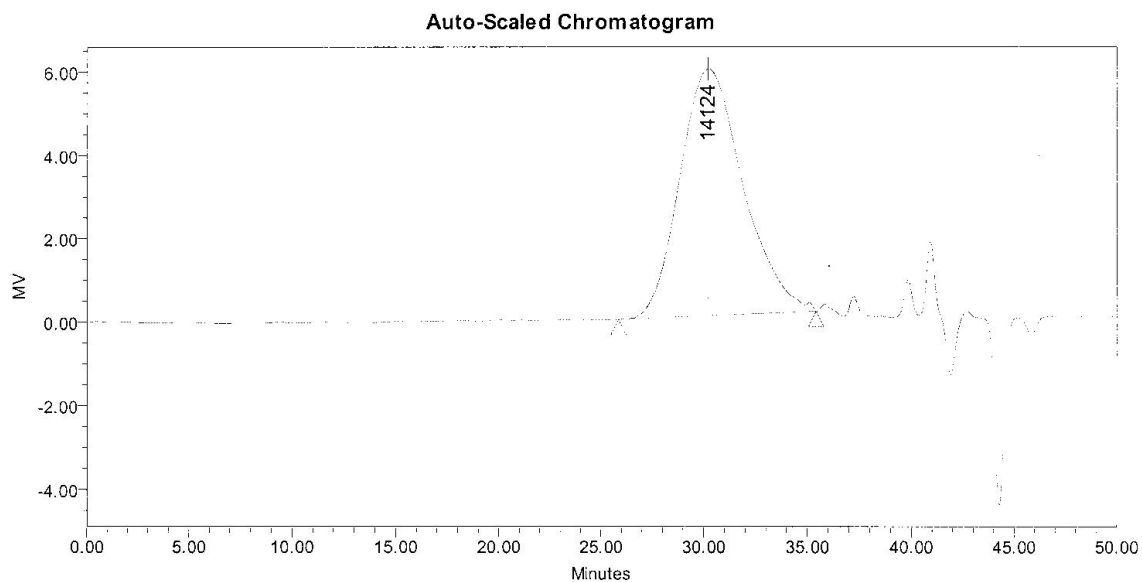


GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Poly dispersity	K	alpha
1		2308	3807		3462	5433	6977	1.649537		

Poly(DEA : OD) GPC

SAMPLE INFORMATION			
Sample Name:	ab5-33a	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	070720
Vial:	116	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	7/20/2007 4:28:27 PM EDT		
Date Processed:	7/23/2007 9:49:20 AM EDT		

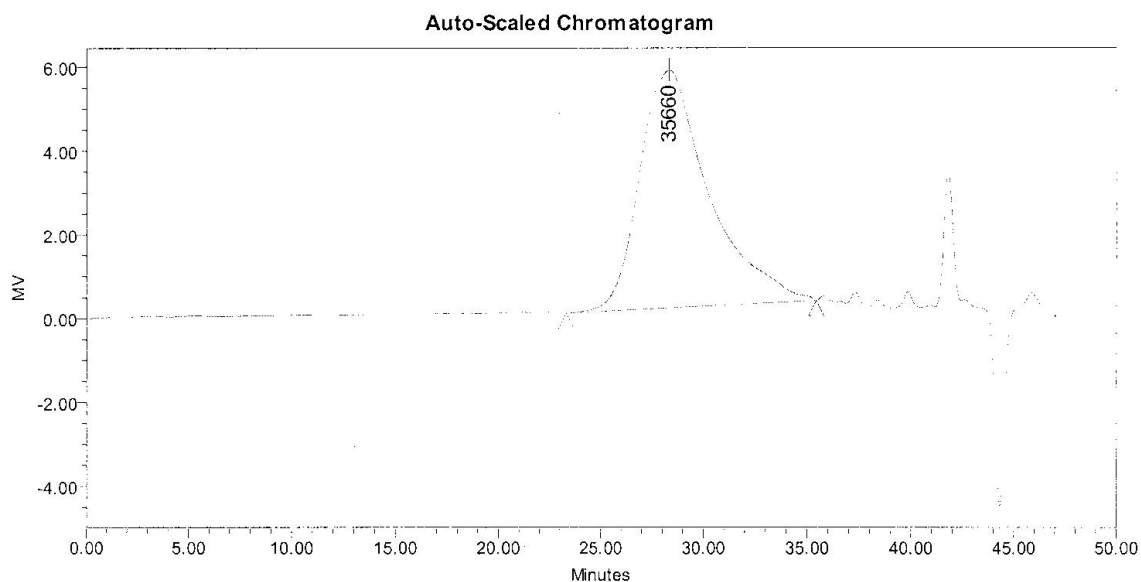


GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		9011	15309		14124	22781	30909	1.698934		

Poly(N₃A : DEA : OD) (10 : 90 : 100) GPC

SAMPLE INFORMATION			
Sample Name:	AB5-42	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	070820
Vial:	72	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	8/20/2007 2:20:39 PM EDT		
Date Processed:	8/21/2007 8:21:39 AM EDT		

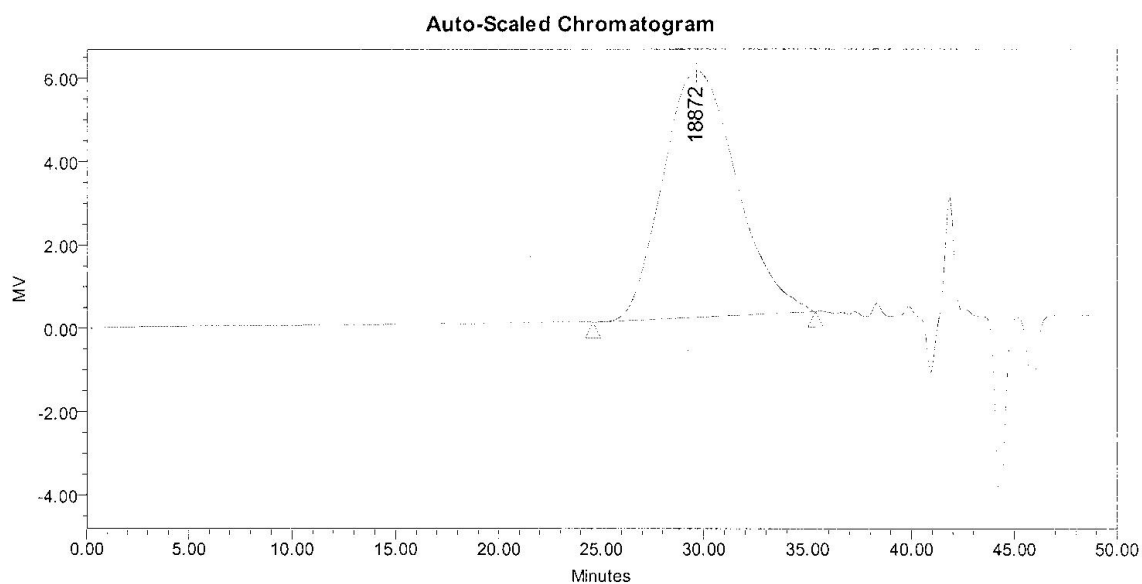


GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		16177	37282		35660	62204	94574	2.304643		

Poly(N₃A : DEA : OD) (25 : 75 : 100) GPC

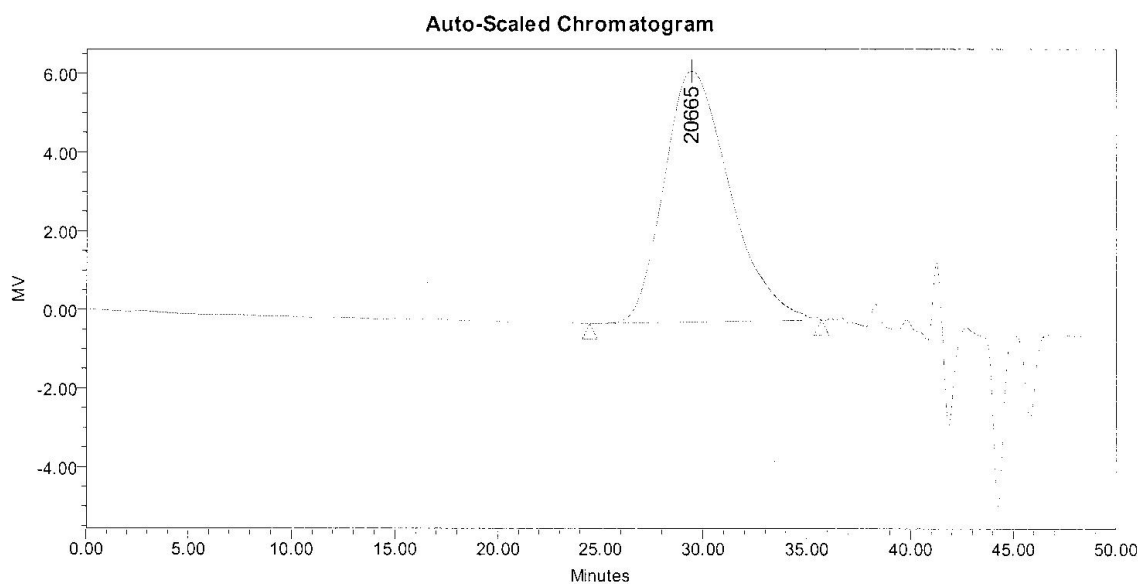
SAMPLE INFORMATION			
Sample Name:	AB5-41	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	070820
Vial:	71	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	8/20/2007 1:29:14 PM EDT		
Date Processed:	8/21/2007 8:20:47 AM EDT		



GPC Results									
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K alpha
1		11290	21795		18872	35728	51125	1.930411	

Poly(N₃A : DEA : OD) (50 : 50 : 100) GPC

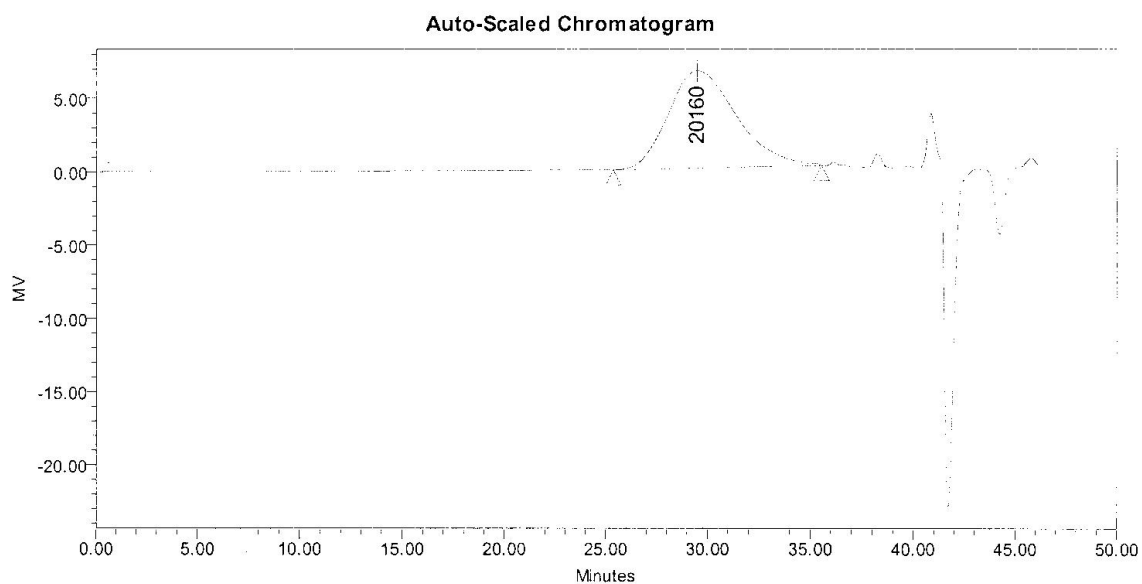
SAMPLE INFORMATION			
Sample Name:	ab5-36	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	070731
Vial:	2	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	7/31/2007 1:13:26 PM EDT		
Date Processed:	8/1/2007 7:42:36 AM EDT		



GPC Results										
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		11733	21492		20665	33026	46519	1.831733		

Poly(N₃A : DEA : OD) (75 : 25 : 100) GPC

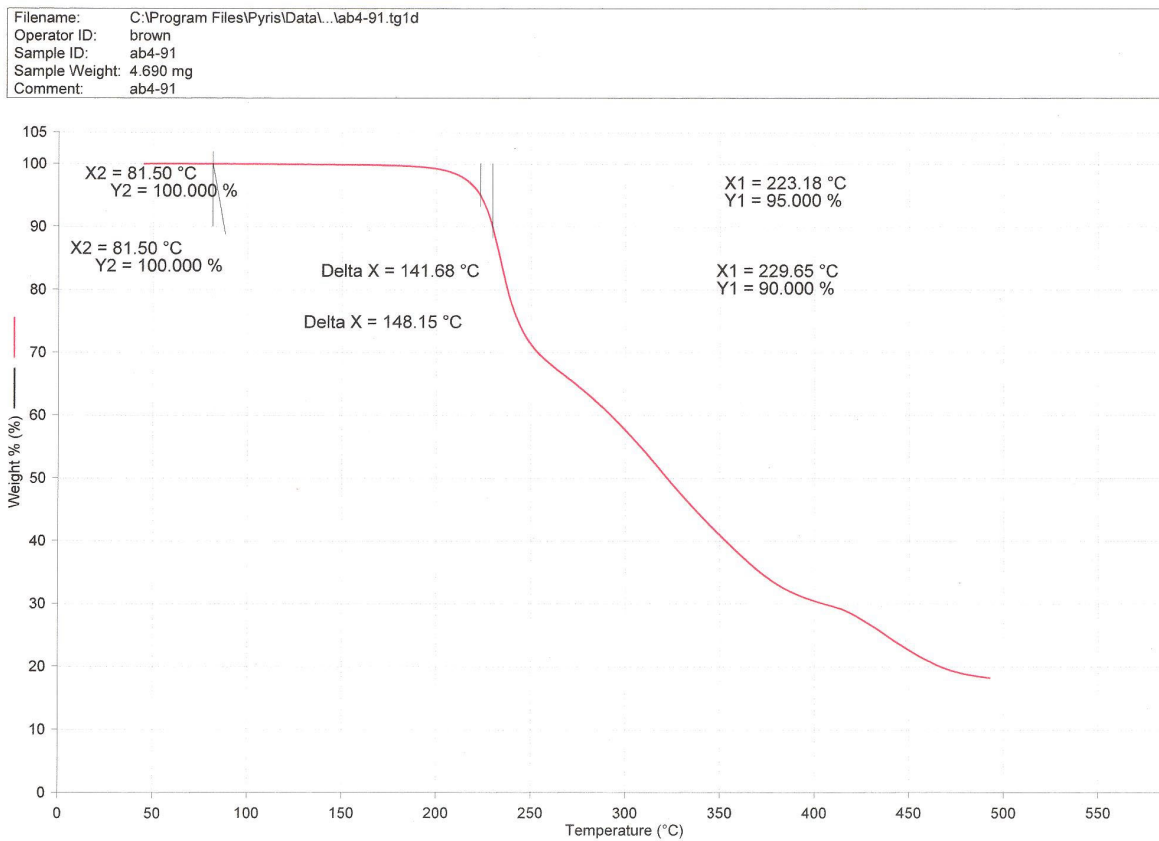
SAMPLE INFORMATION			
Sample Name:	AB5-40	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	070806
Vial:	31	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	8/6/2007 3:44:35 PM EDT		
Date Processed:	8/6/2007 5:17:20 PM EDT		



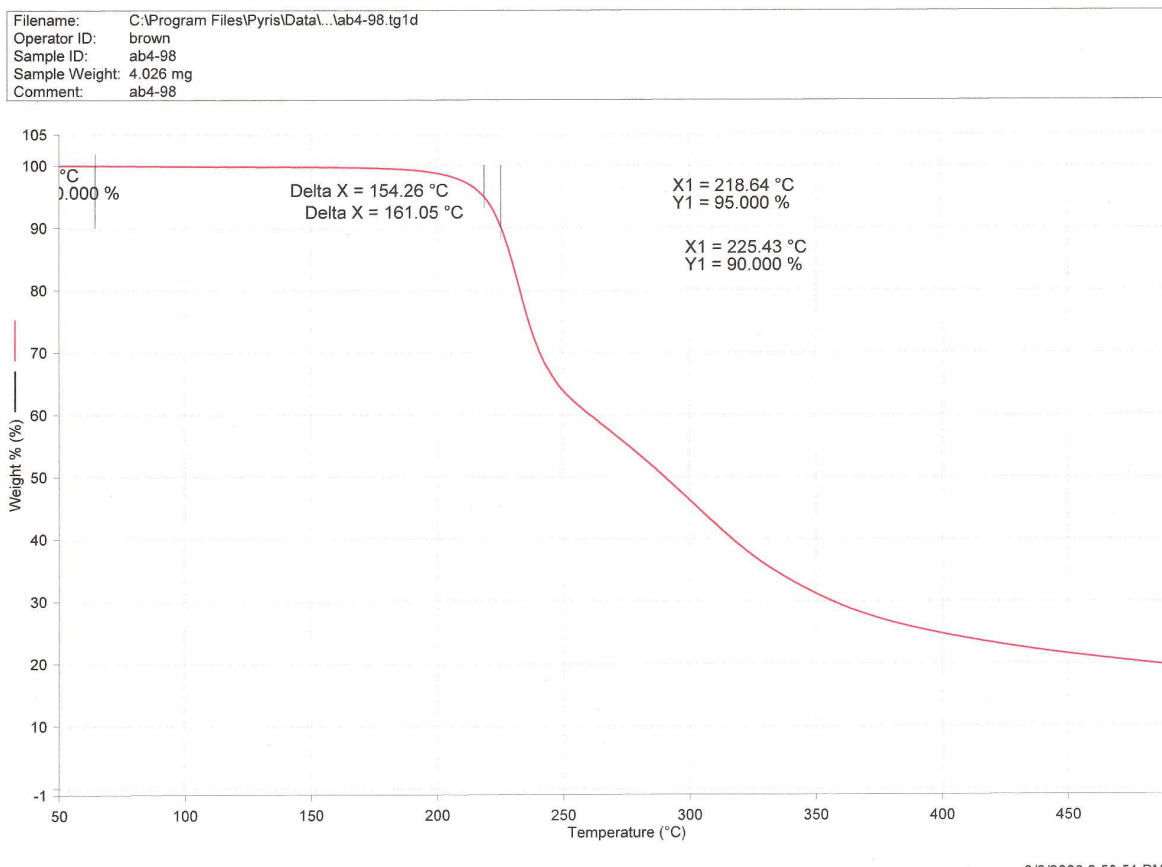
GPC Results										
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		11294	21321		20160	33523	46961	1.887859		

Representative TGA chromatograms

Polyester 1

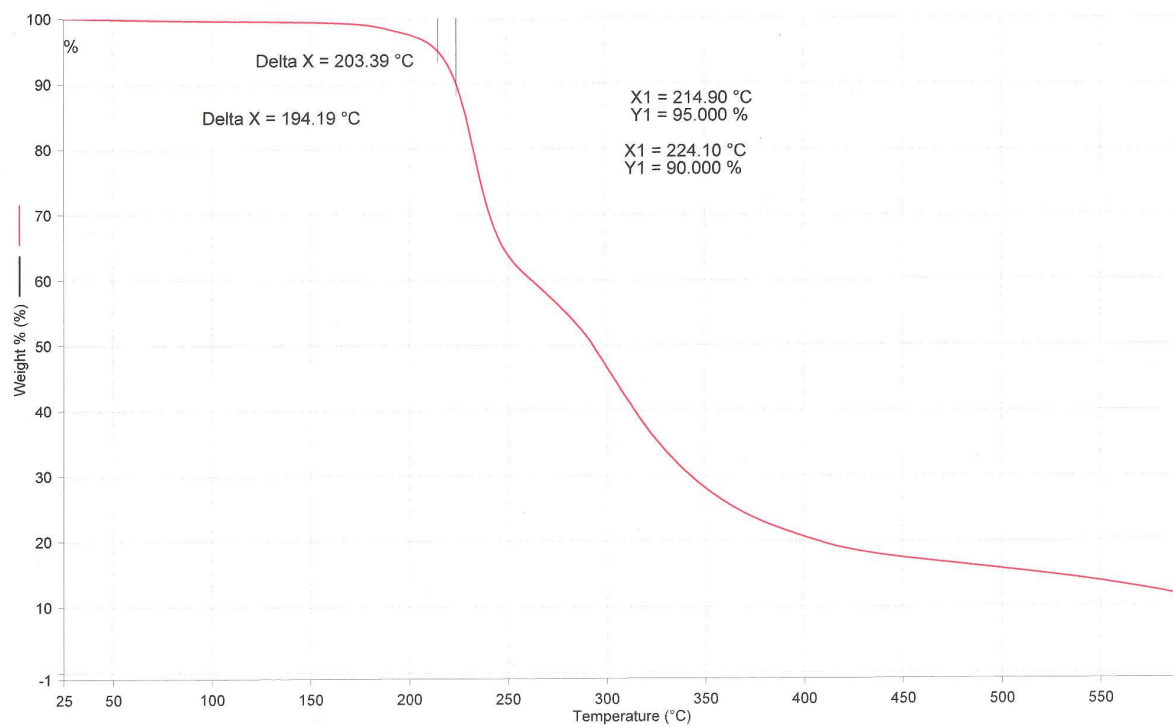


Polyester 2 TGA

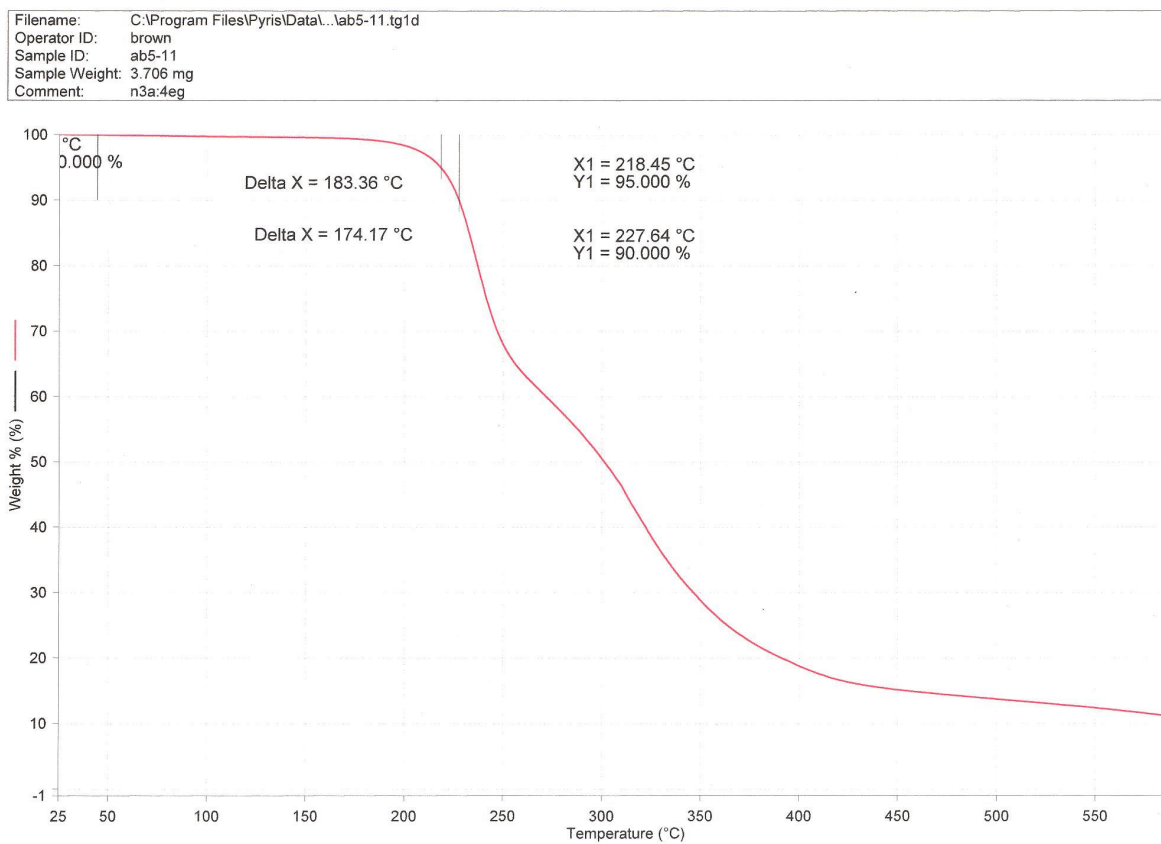


Polyester 3 TGA

Filename: C:\Program Files\Pyris\Data\...\ab5-10.tg1d
Operator ID: brown
Sample ID: ab5-10
Sample Weight: 3.765 mg
Comment: n3a:3eg



Polyester 4 TGA



Representative DSC chromatograms

Polyester 1

<< DSC >>

Data Name: ab4-91

Date: 7/ 5/22 10:45

Sample: ab4-91

1 mg

Reference: aluminum reference

0 mg

Temperature Program:

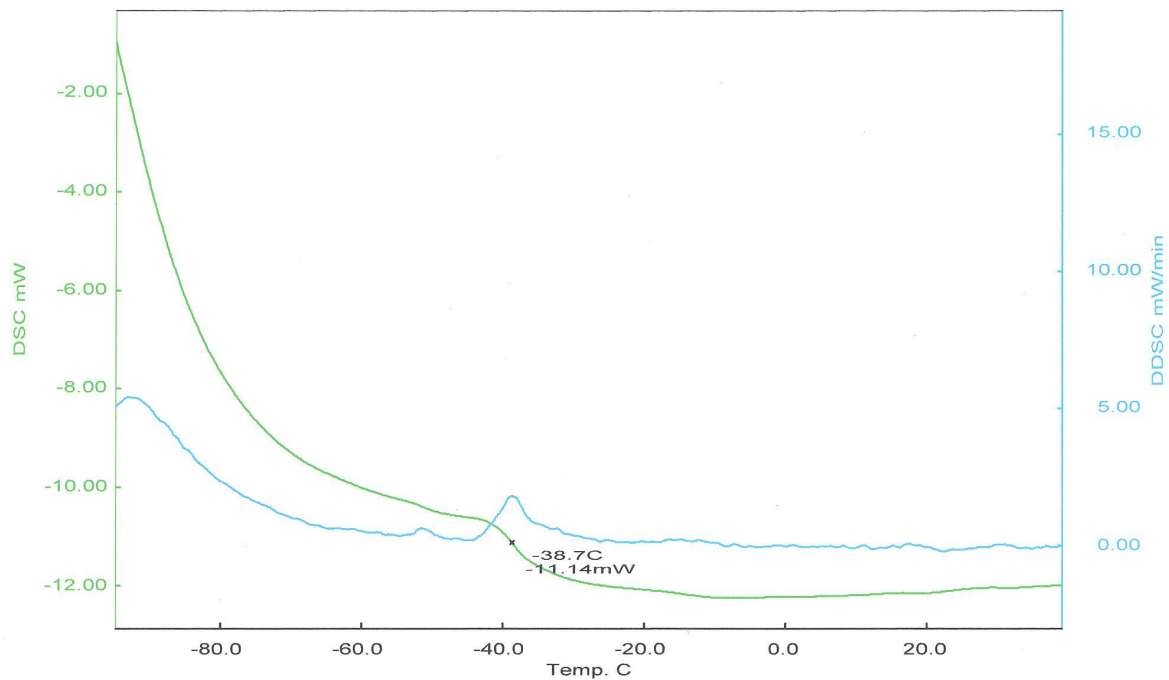
	[C]	[C/min]	[min]	[sec]
1*	25 - 50	10	5	0.5
2*	50 - -100	10	10	0.5
3*	-100- 50	10	5	0.5
4*	50 - -100	10	10	0.5
5*	-100- 50	10	5	0.5
6*	50 - 25	25	1	0.5

Comments:

Operator brown

ab4-91

n3a:od



Polyester 2 DSC

<< DSC >>

Data Name: ab4-98

Date: 7/ 5/22 11:39

Sample: ab4-98

Reference: aluminum reference

1 mg

0 mg

Temperature Program:

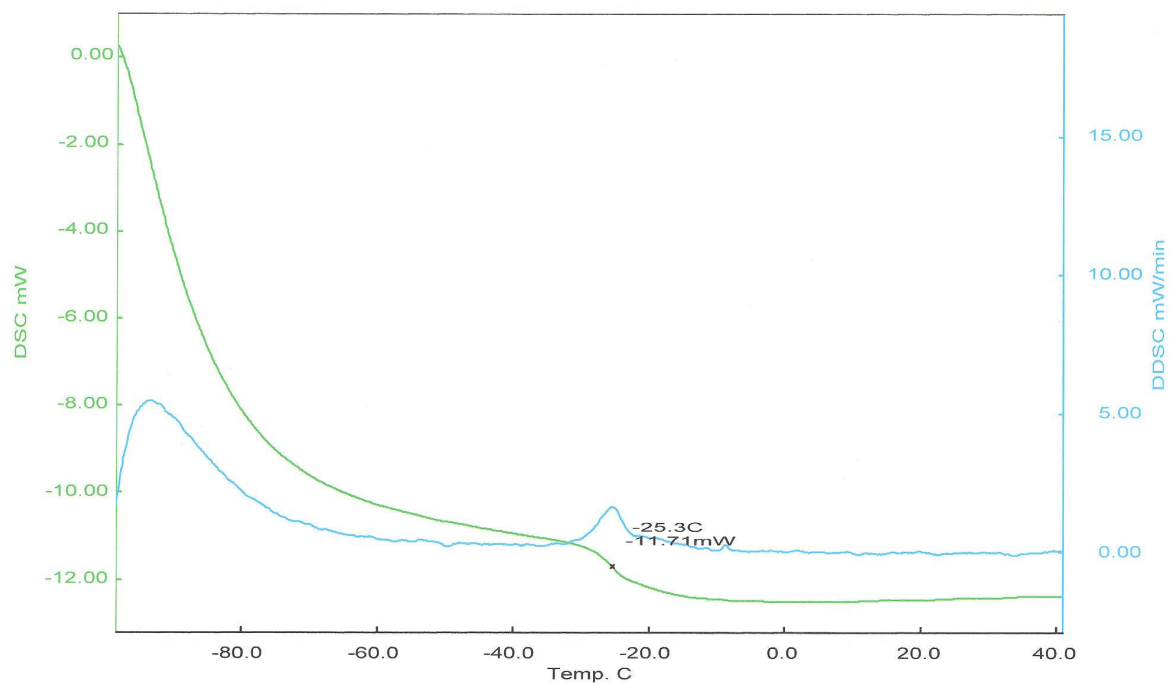
	[C]	[C/min]	[min]	[sec]
1*	25	-	50	10
2*	50	-	-100	10
3*	-100	-	50	10

Comments:

Operator brown

ab4-91

n3a:2eg



Polyester 3 DSC

<< DSC >>

Data Name: ab5-10

Date: 7/6/12 9:26

Sample: ab5-10

10.5 mg

Reference: aluminum reference

0 mg

Temperature Program:

[C] [C/min] [min] [sec]

1* 25 - 50 10 5 0.5

2* 50 - -125 10 10 0.5

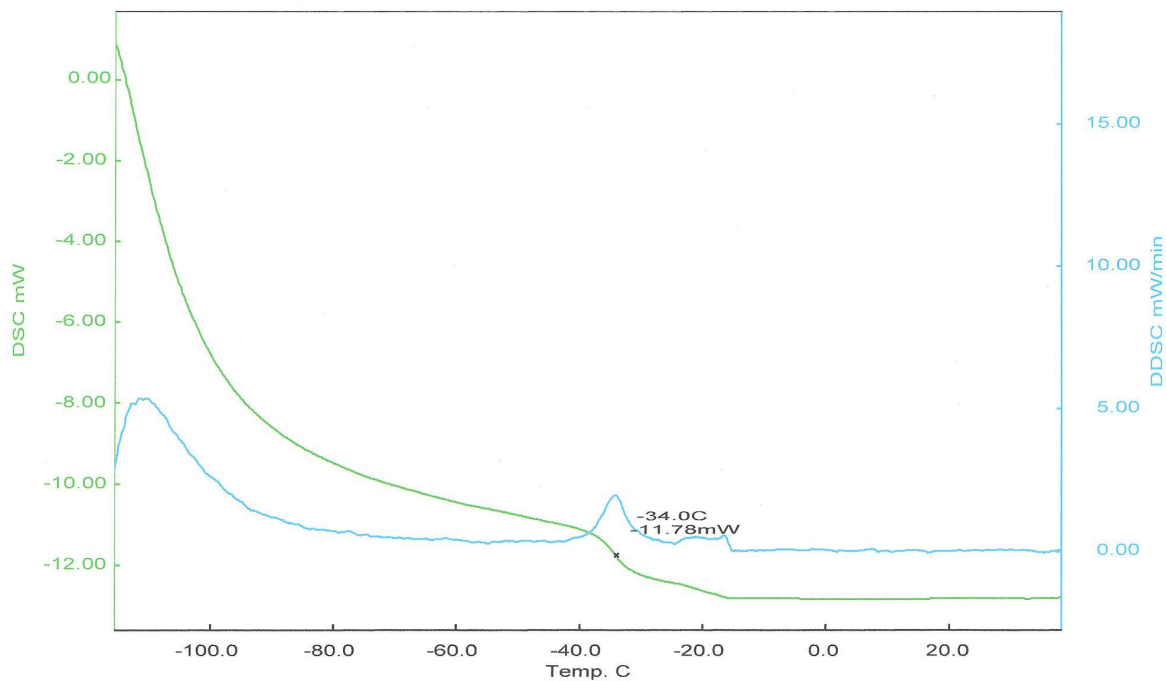
3* -125- 50 10 5 0.5

4* 50 - 25 25 2 0.5

Comments:

Operator brown

n3a 3eg



Polyester 4 DSC

<< DSC >>

Data Name: ab5-11

Date: 7/6/12 10:50

Sample: ab5-11

3.7 mg

Reference: aluminum reference

0 mg

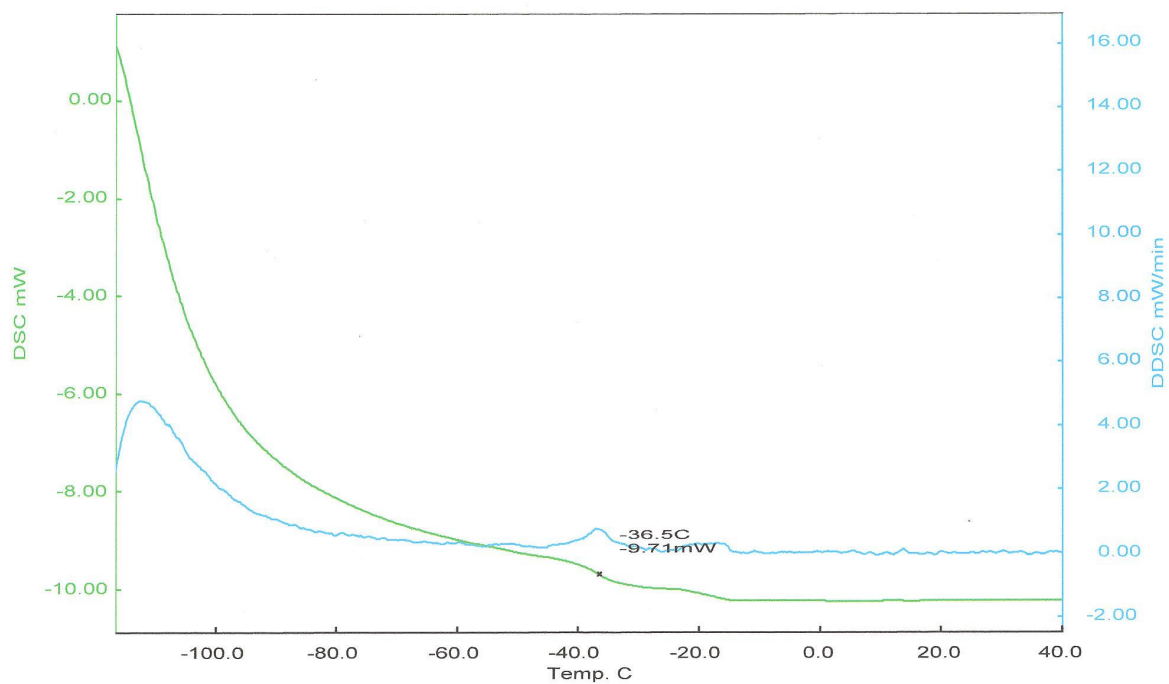
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-50	10	5
2*	50	-125	10	10
3*	-125	50	10	5
4*	50	-25	25	2

Comments:

Operator brown

n3a 4eg



Poly(DEA : OD) DSC

<< DSC >>

Data Name: ab5-23a

Date: 7/ 7/ 7 15:44

Sample: ab5-23

8 mg

Reference: aluminum reference

0 mg

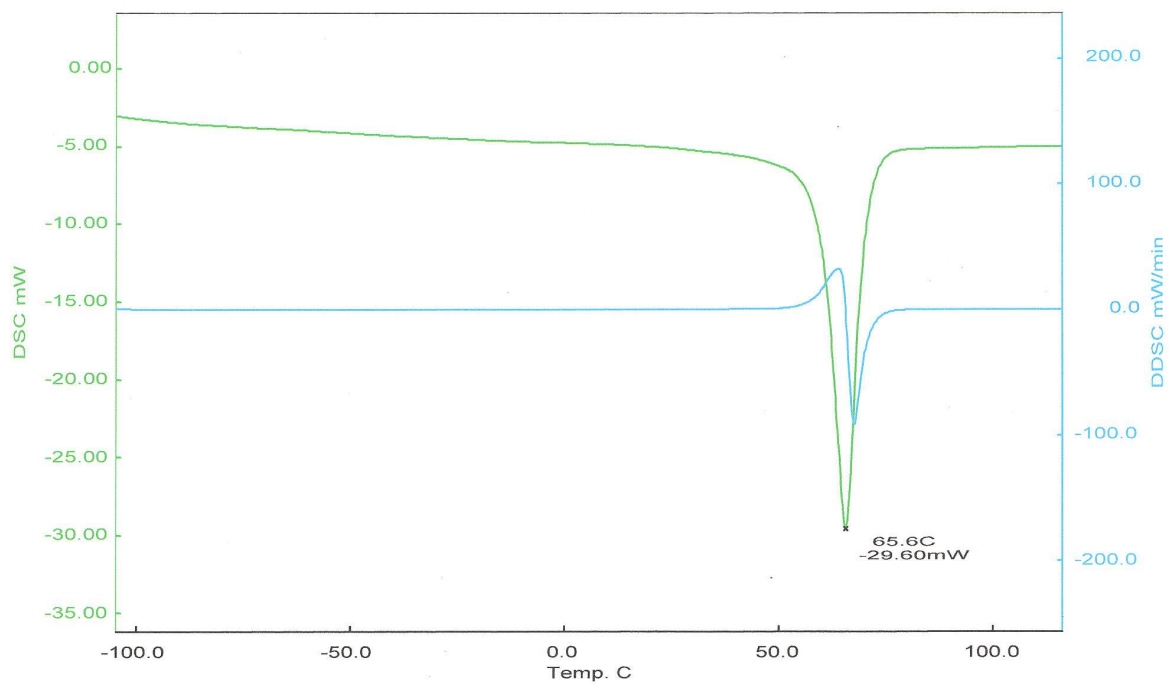
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25 -	125	10	5 0.5
2*	125 -	-125	10	10 0.5
3*	-125 -	125	10	5 0.5
4*	125 -	25	30	5 0.5

Comments:

Operator Brown

dea:od



Poly(N₃A : DEA : OD) (10 : 90 : 100) DSC

<< DSC >>

Data Name: ab5-24a

Date: 7/ 7/ 8 17:46

Sample: ab5-24

7.7 mg

Reference: aluminum reference

0 mg

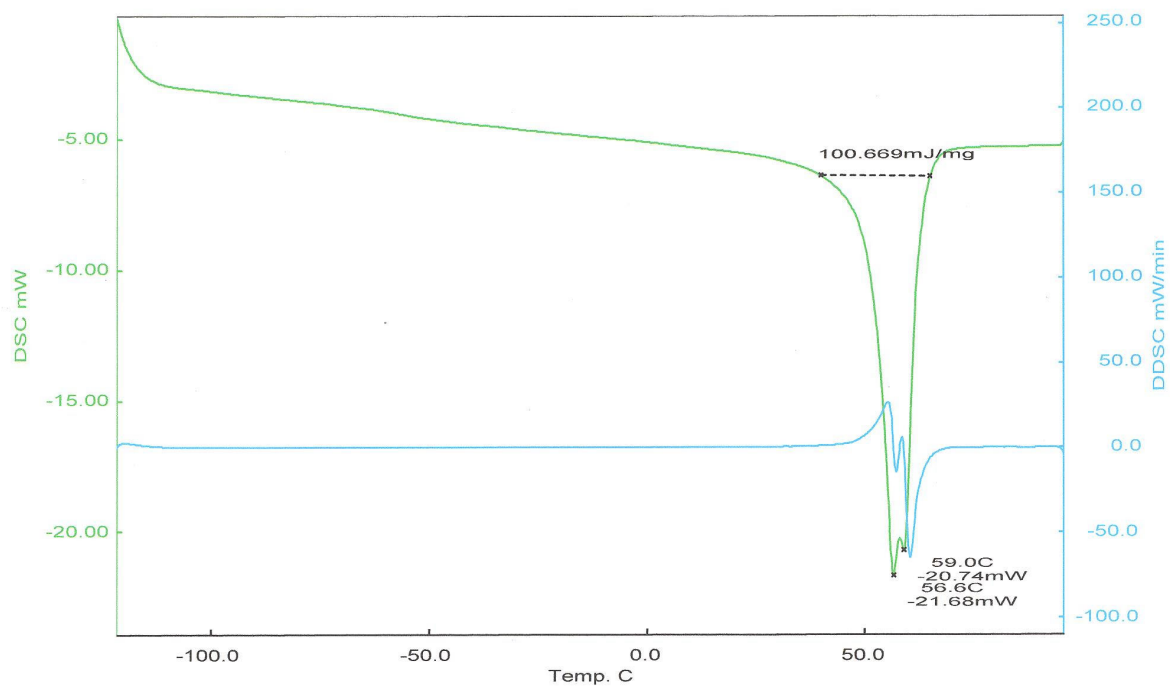
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25 - 100	10	5	0.5
2*	100 - -150	10	10	0.5
3*	-150 - 100	10	5	0.5
4*	100 - 25	30	5	0.5

Comments:

Operator steven b

poly click



<< DSC >>

Data Name: ab5-24a

Date: 7/7/8 17:46

Sample: ab5-24

7.7 mg

Reference: aluminum reference

0 mg

Temperature Program:

	[C]	[C/min]	[min]	[sec]
--	-----	---------	-------	-------

1*	25	-	100	10	5	0.5
----	----	---	-----	----	---	-----

2*	100	-	150	10	10	0.5
----	-----	---	-----	----	----	-----

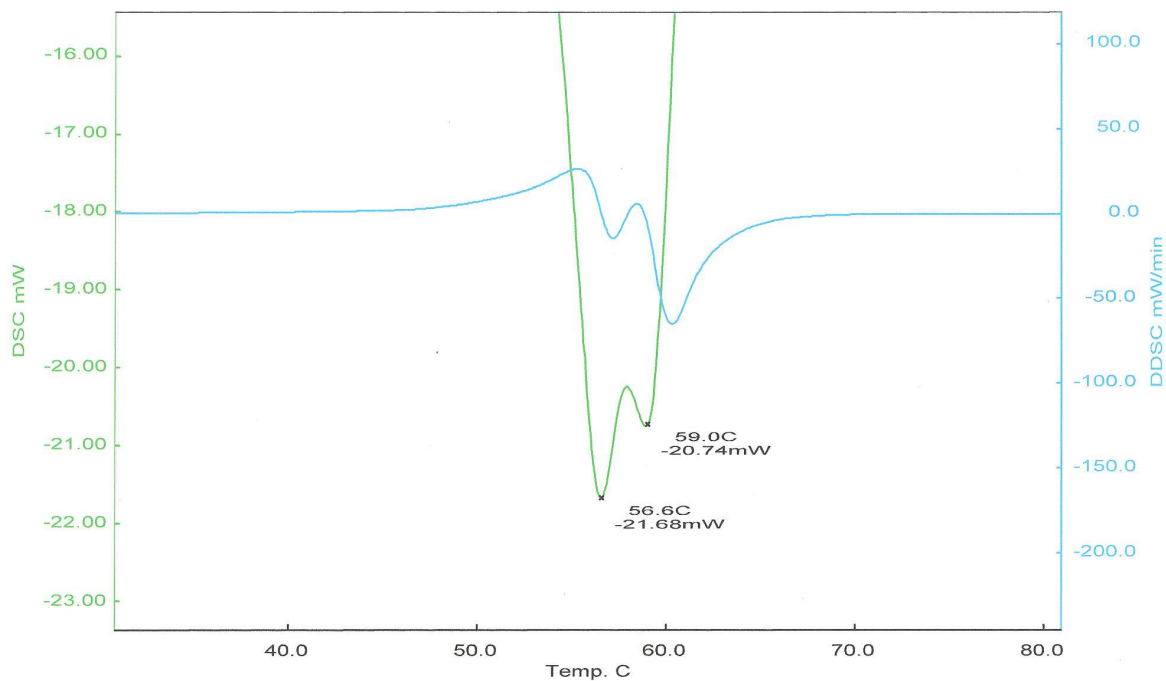
3*	-150	-	100	10	5	0.5
----	------	---	-----	----	---	-----

4*	100	-	25	30	5	0.5
----	-----	---	----	----	---	-----

Comments:

Operator steven b

poly click



Poly(N₃A : DEA : OD) (25 : 75 : 100) DSC

<< DSC >>

Data Name: AB5-22a

Date: 7/ 7/ 5 18:26

Sample: AB5-22

Reference: aluminum reference

4 mg

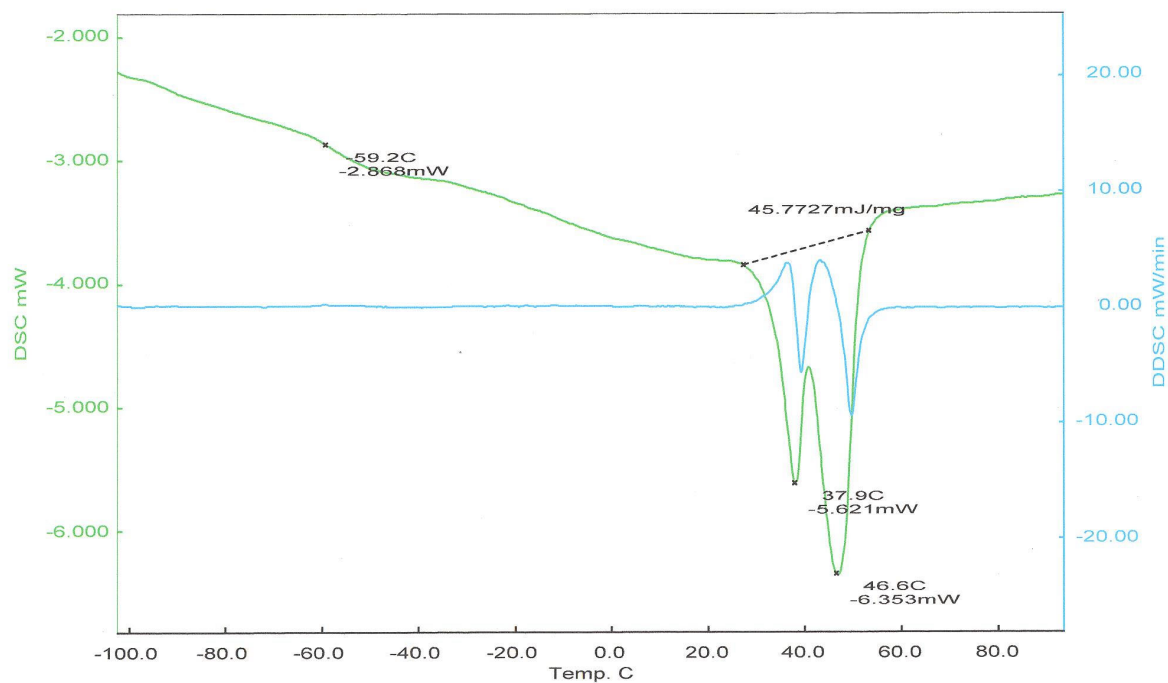
0 mg

Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-	100	10
2*	100	-	150	10
3*	100	-	150	10
4*	100	-	150	10
5*	100	-	150	10
6*	100	-	150	10

Comments:

Operator ahb



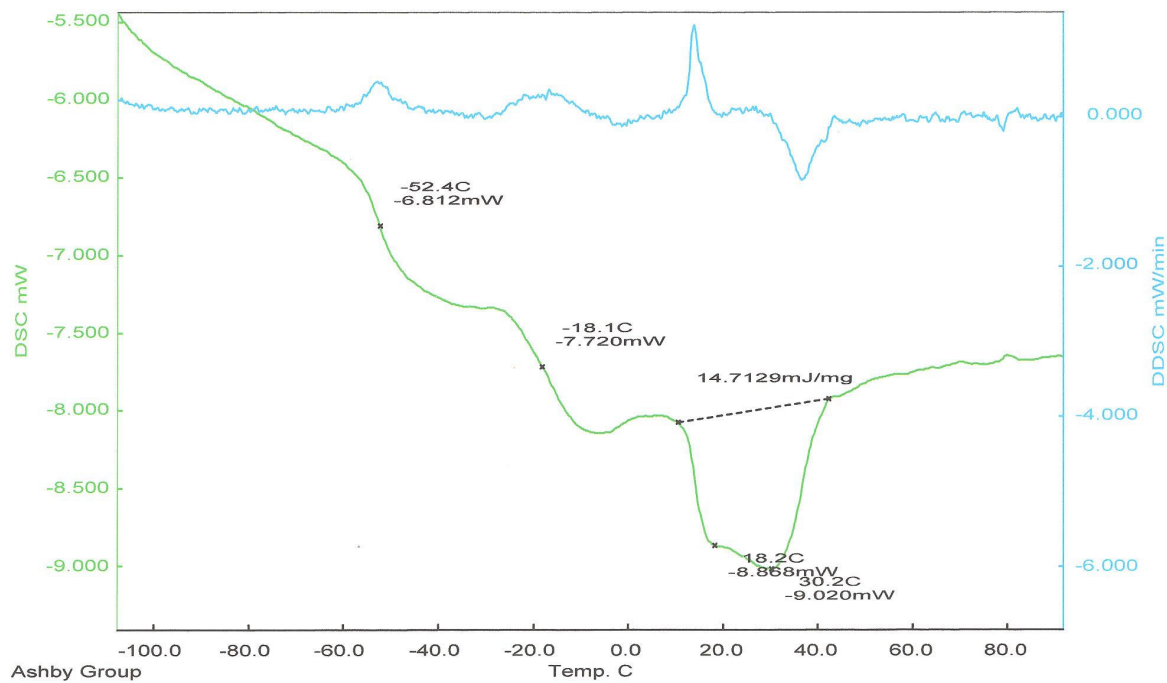
Poly(N₃A : DEA : OD) (50 : 50 : 100) DSC

<< DSC >>
 Data Name: ab5-19c
 Date: 7/12/13 12:15
 Sample: ab5-19c
 Reference: Aluminum Liquid
 0 mg

Temperature Program:
 [C] [C/min] [min] [sec]
 1* 25 - -125 10 10 0.5
 2* -125- 100 5 2 0.5
 3* 100- 25 25 1 0.5

Comments:
 Operator brown
 repeat
 5 deg c / min

17.2 mg



Poly(N₃A : DEA : OD) (75 : 25 : 100) DSC

<< DSC >>

Data Name: AB5-40

Date: 7/ 8/16 10:22

Sample: AB5-40

9.9 mg

Reference: Aluminum Pan

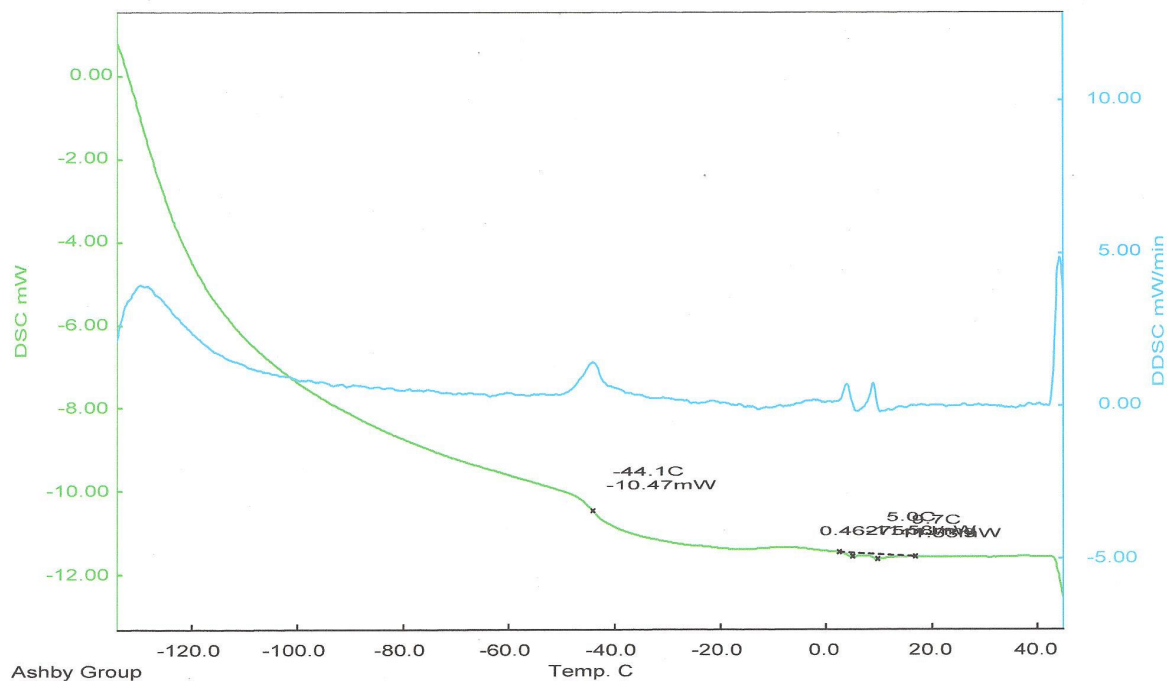
0 mg

Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25	-	50	10 5 0.5
2*	50	-	150	10 20 0.5
3*	-150	-	50	10 5 0.5
4*	50	-	25	30 0 0.5

Comments:

Operator Brown



<< DSC >>

Data Name: AB5-40

Date: 7/8/16 10:22

Sample: AB5-40

Reference: Aluminum Pan

9.9 mg

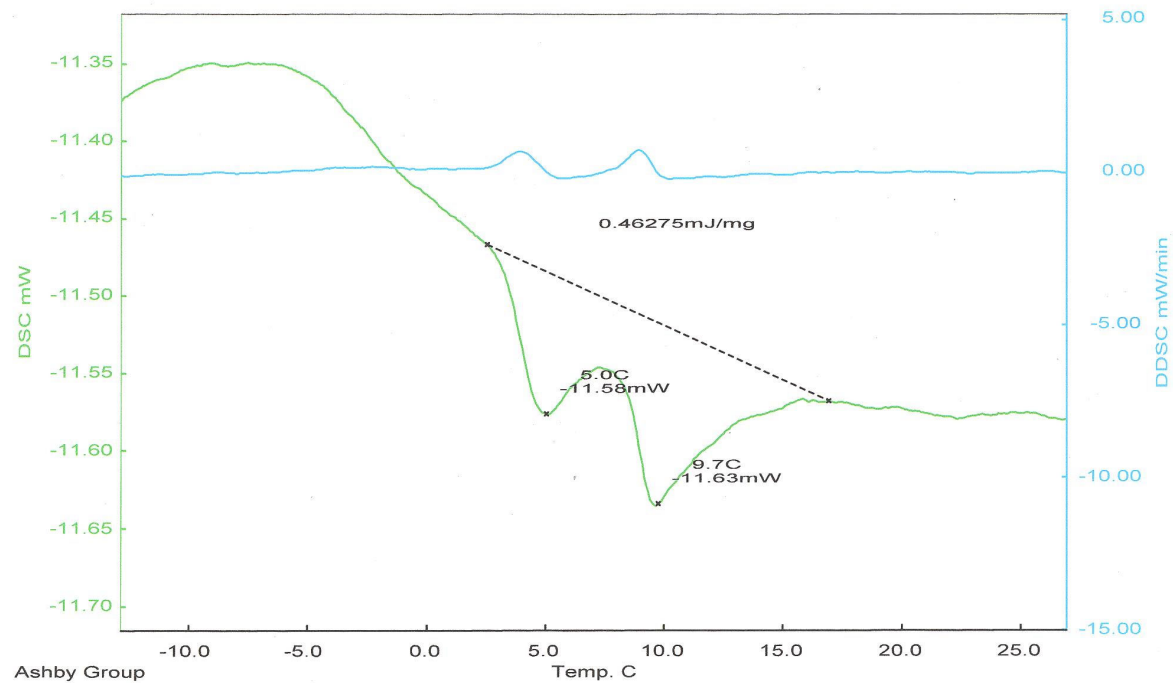
0 mg

Temperature Program:

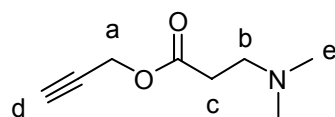
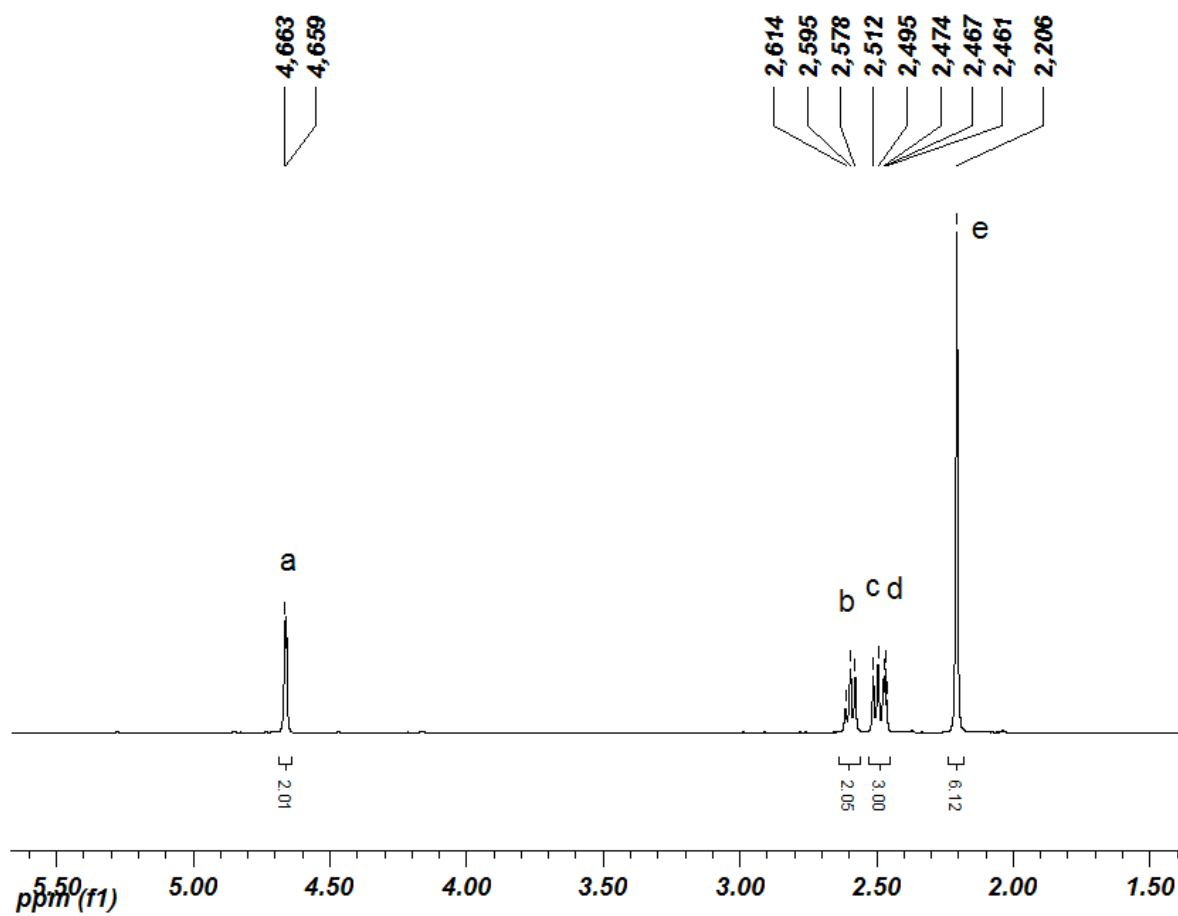
	[C]	[C/min]	[min]	[sec]
1*	25	-50	10	5
2*	50	-150	10	20
3*	-150	-50	10	5
4*	50	-25	30	0

Comments:

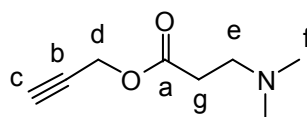
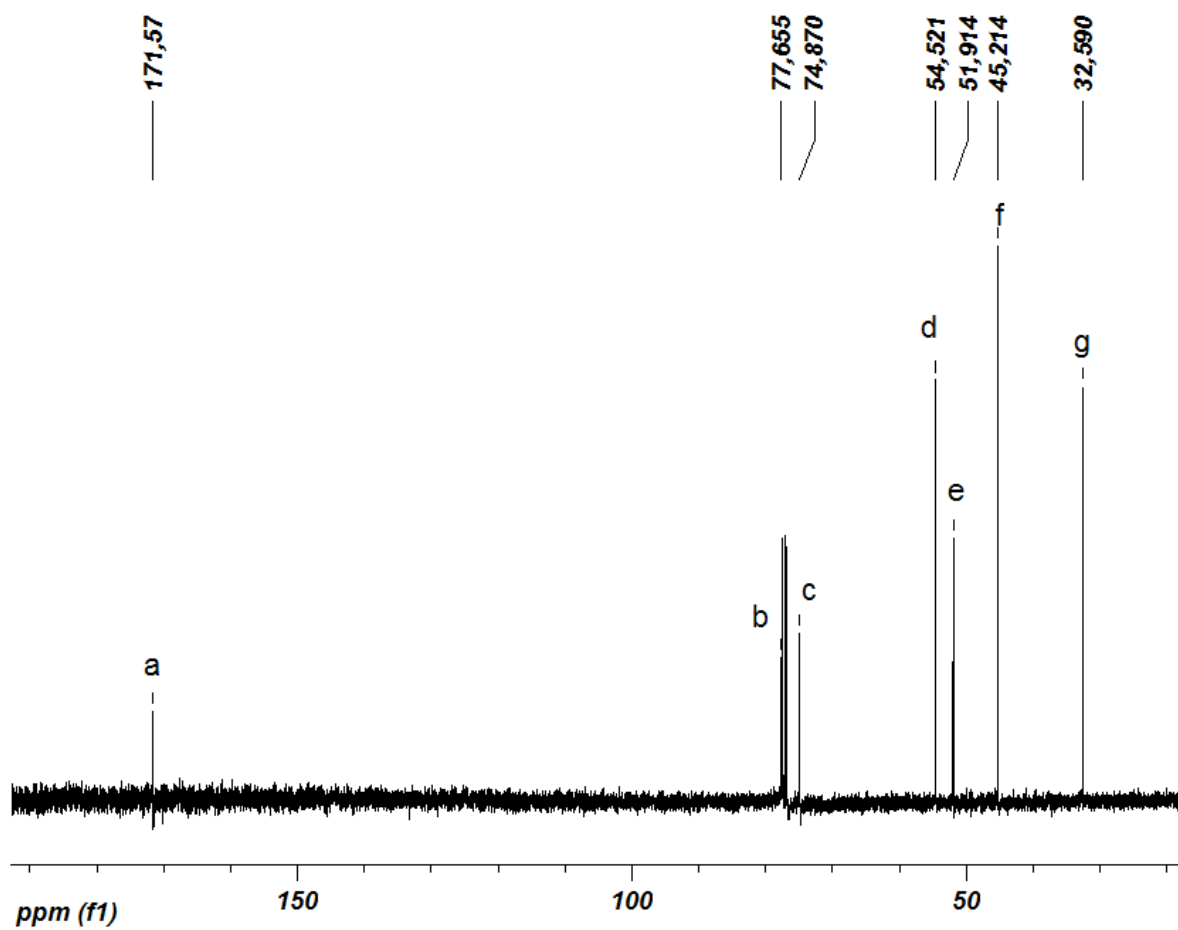
Operator Brown



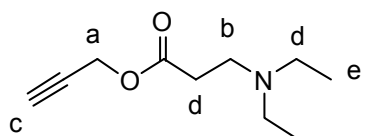
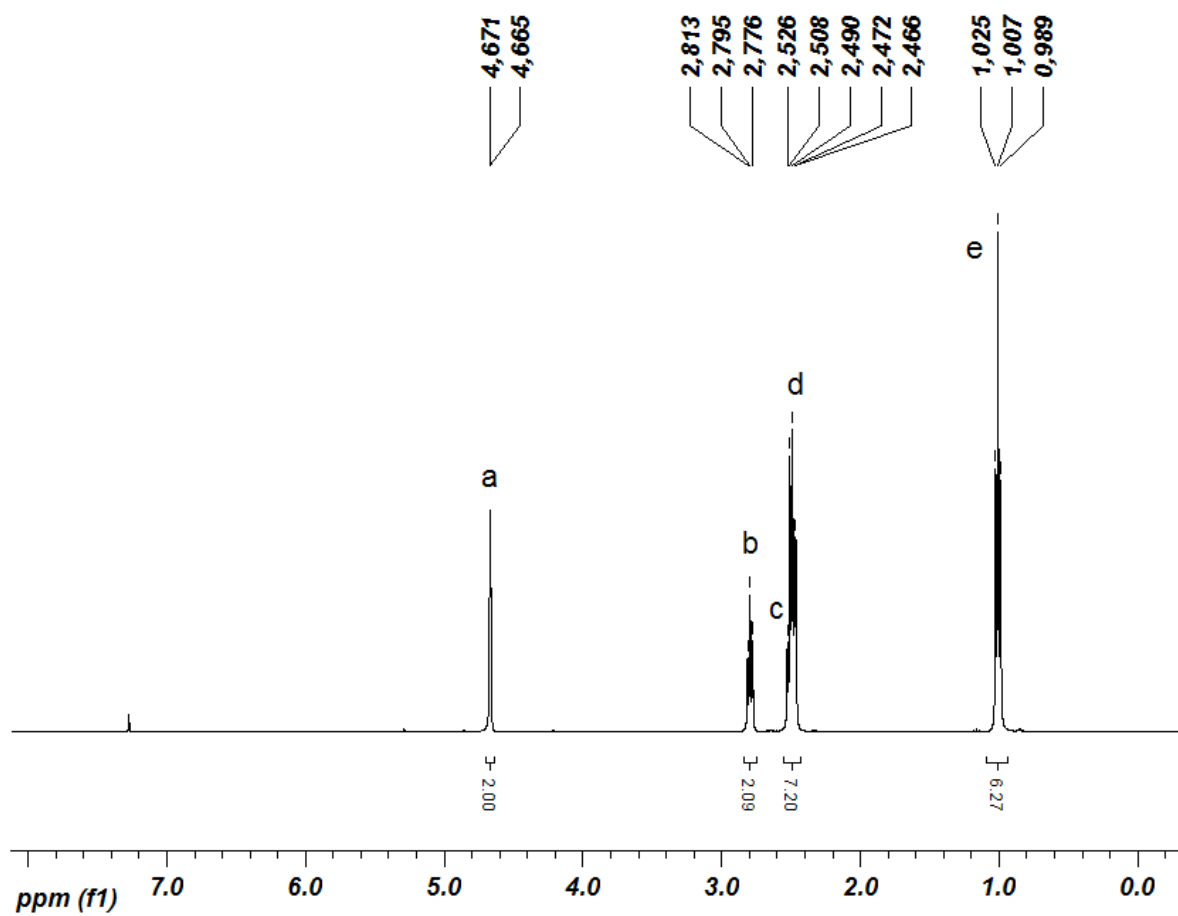
Proton NMR - Propargyl 3-(dimethylamino)propanoate



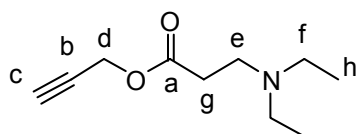
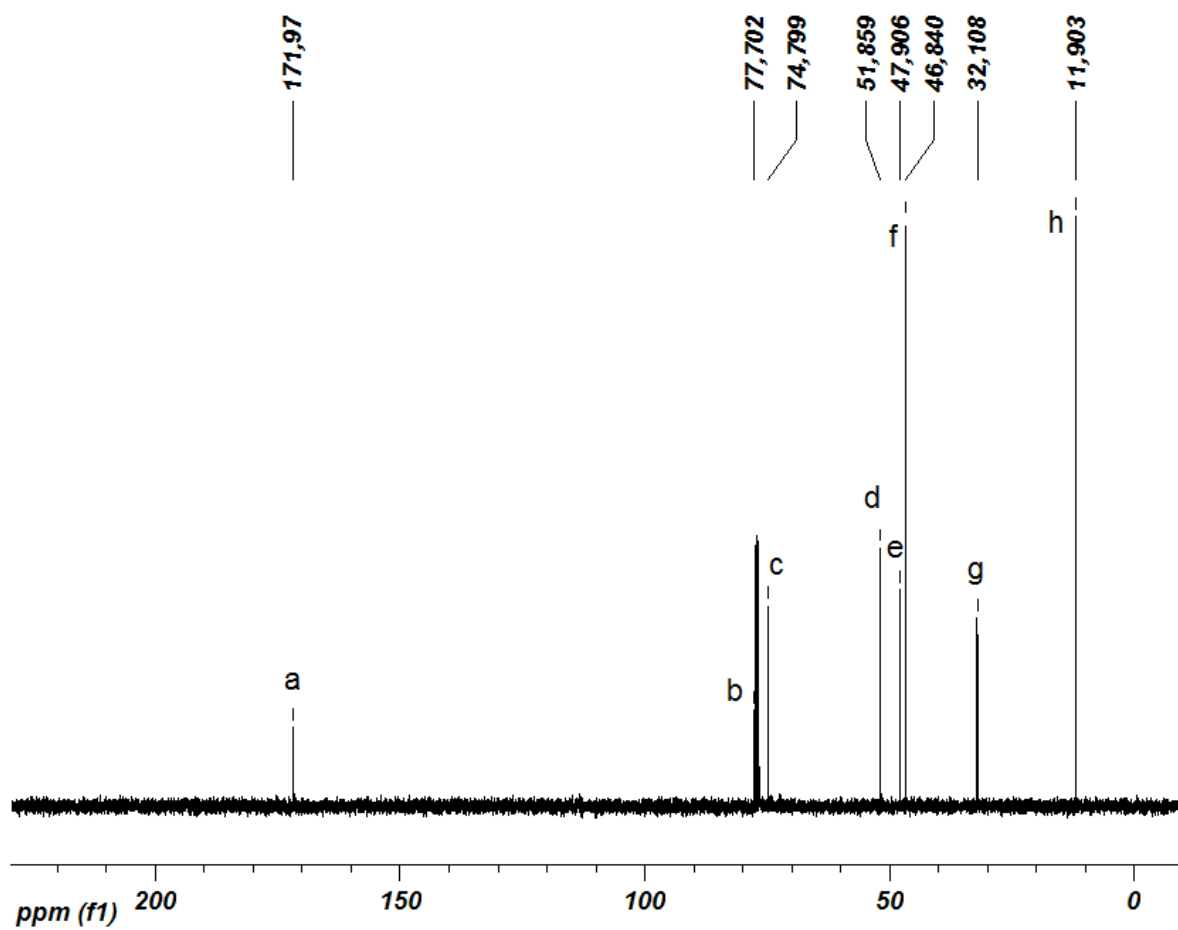
Carbon NMR - Propargyl 3-(dimethylamino)propanoate



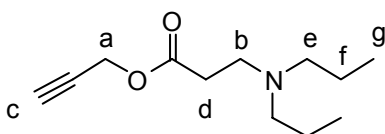
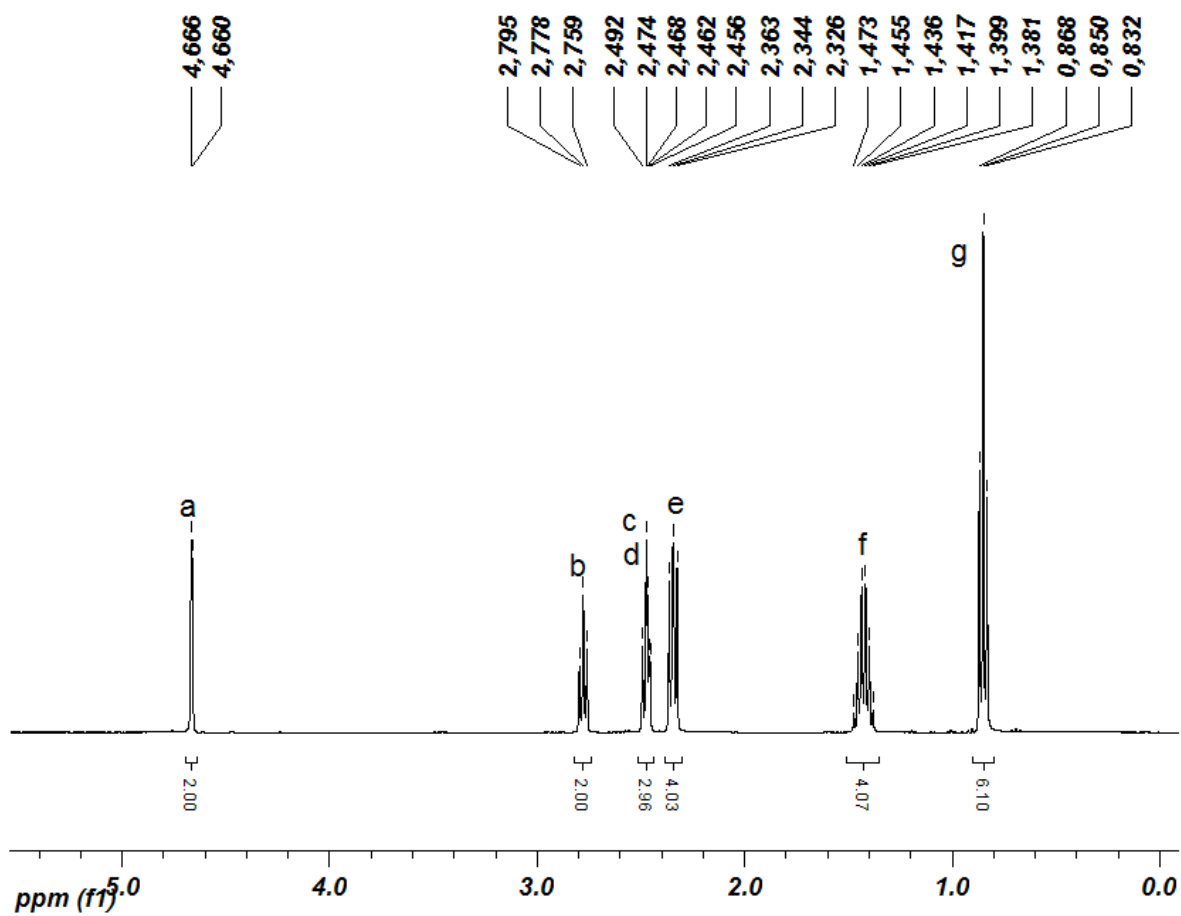
Proton NMR - Propargyl 3-(diethylamino)propanoate



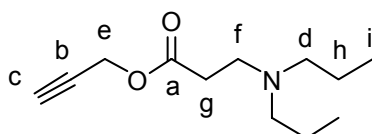
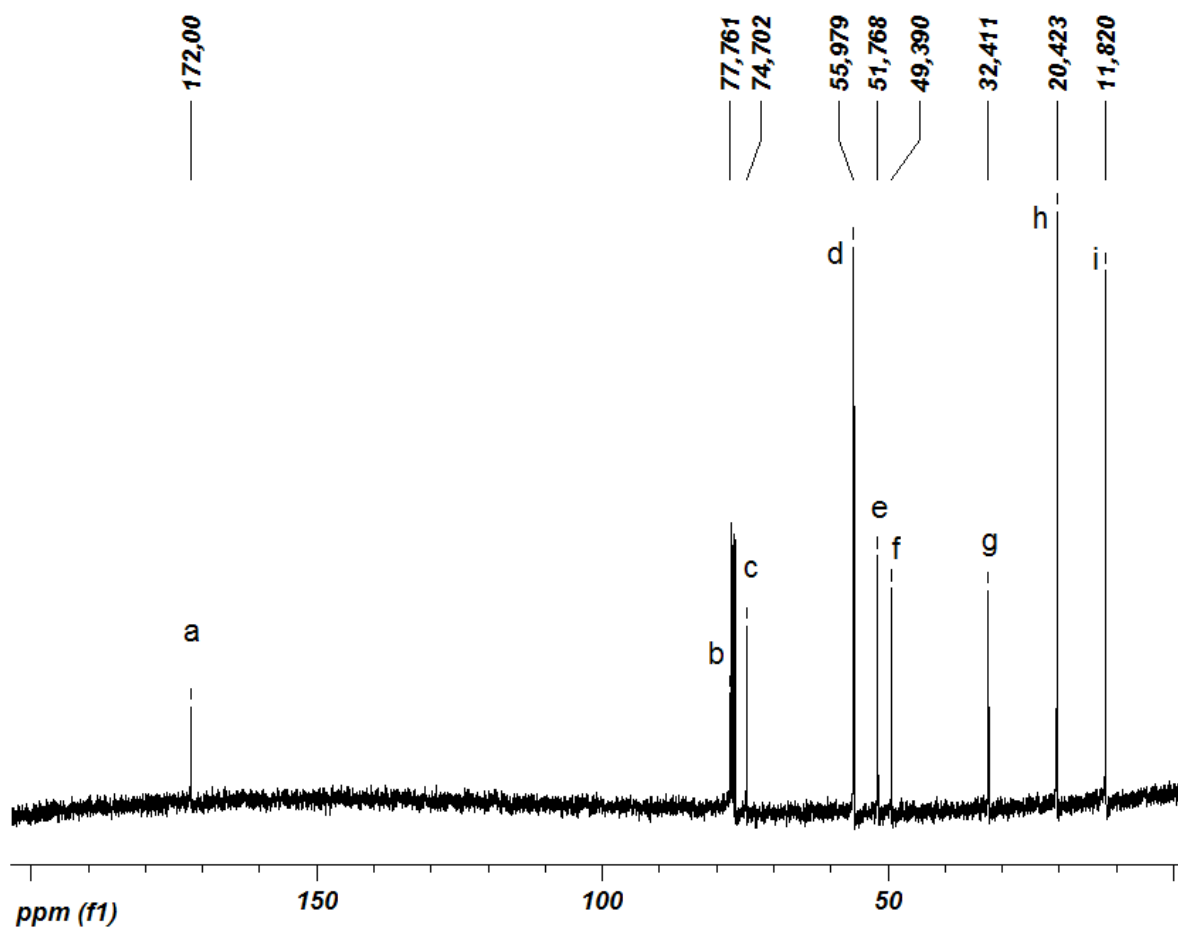
Carbon NMR - Propargyl 3-(diethylamino)propanoate



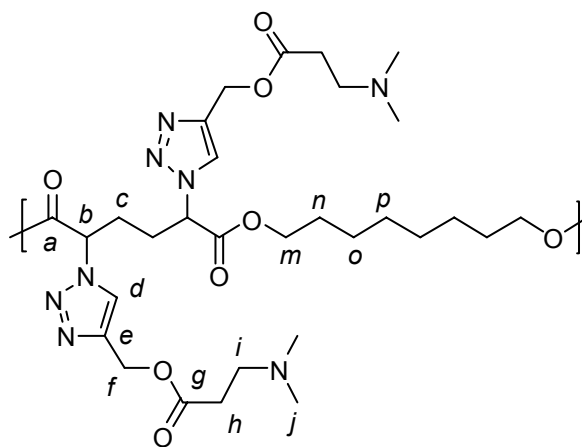
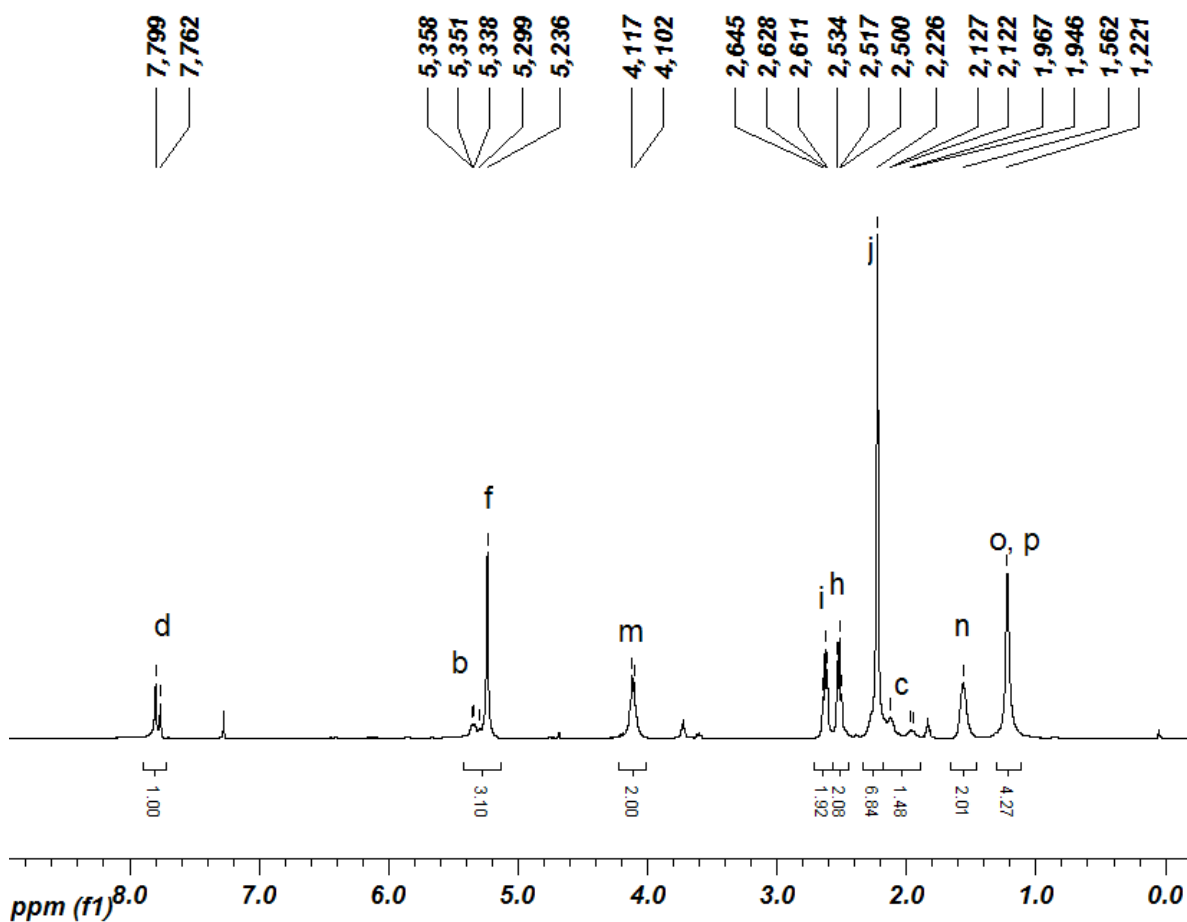
Proton NMR - Propargyl 3-(dipropylamino)propanoate



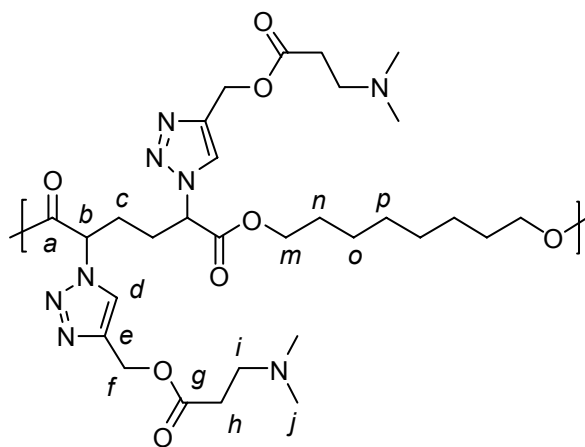
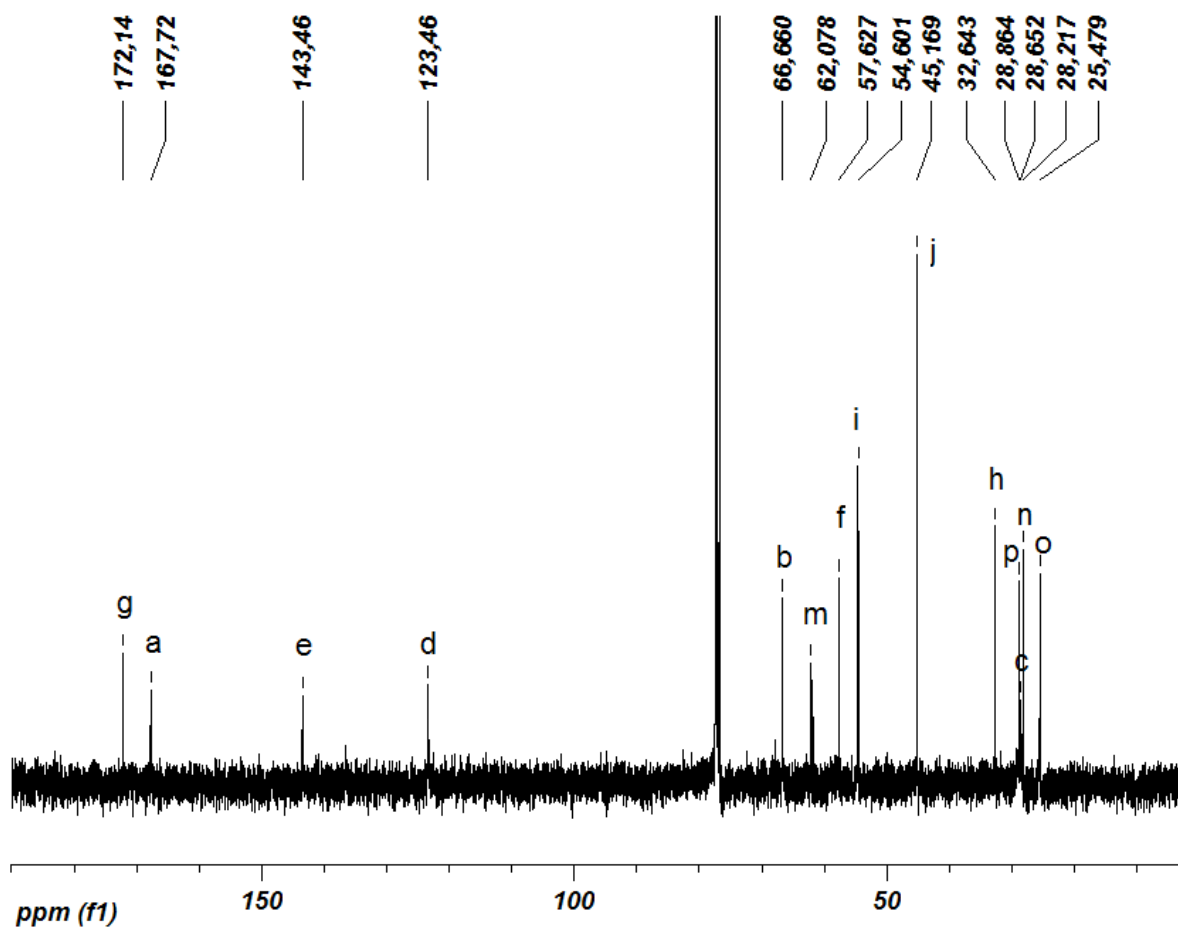
Carbon NMR - Propargyl 3-(dipropylamino)propanoate



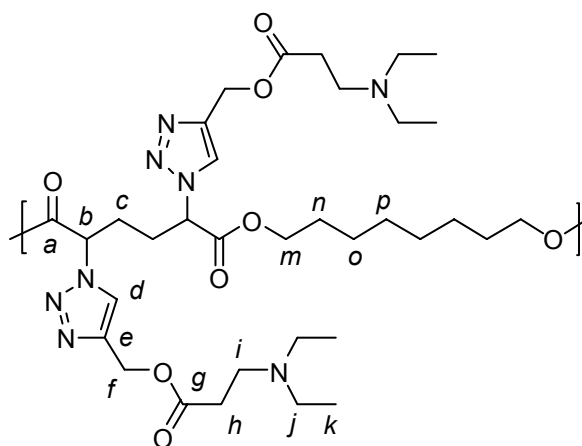
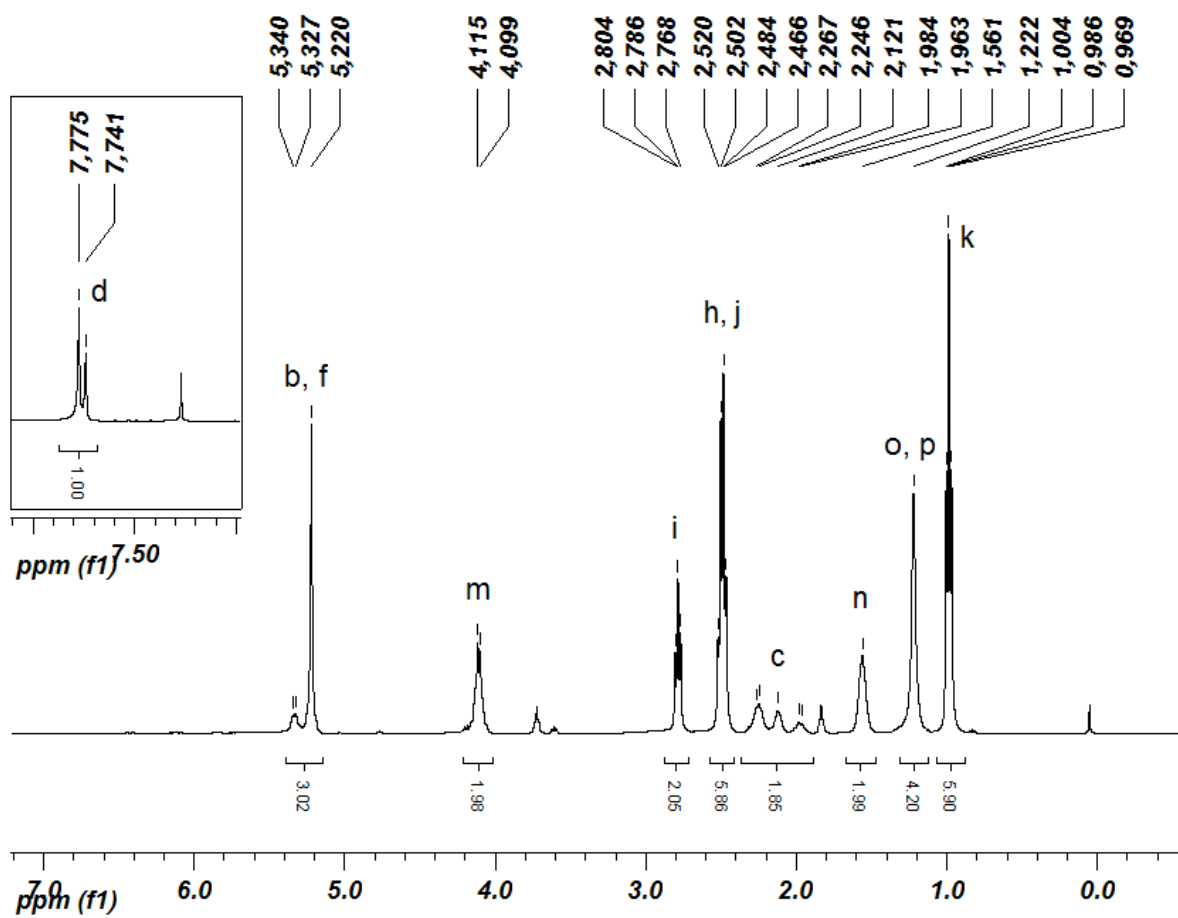
Proton NMR – Dimethylamine-grafted polyester



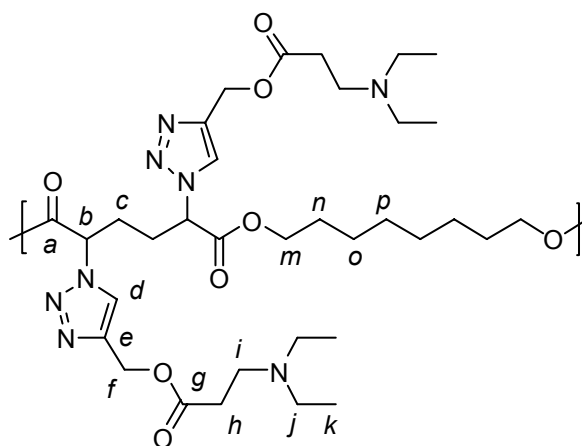
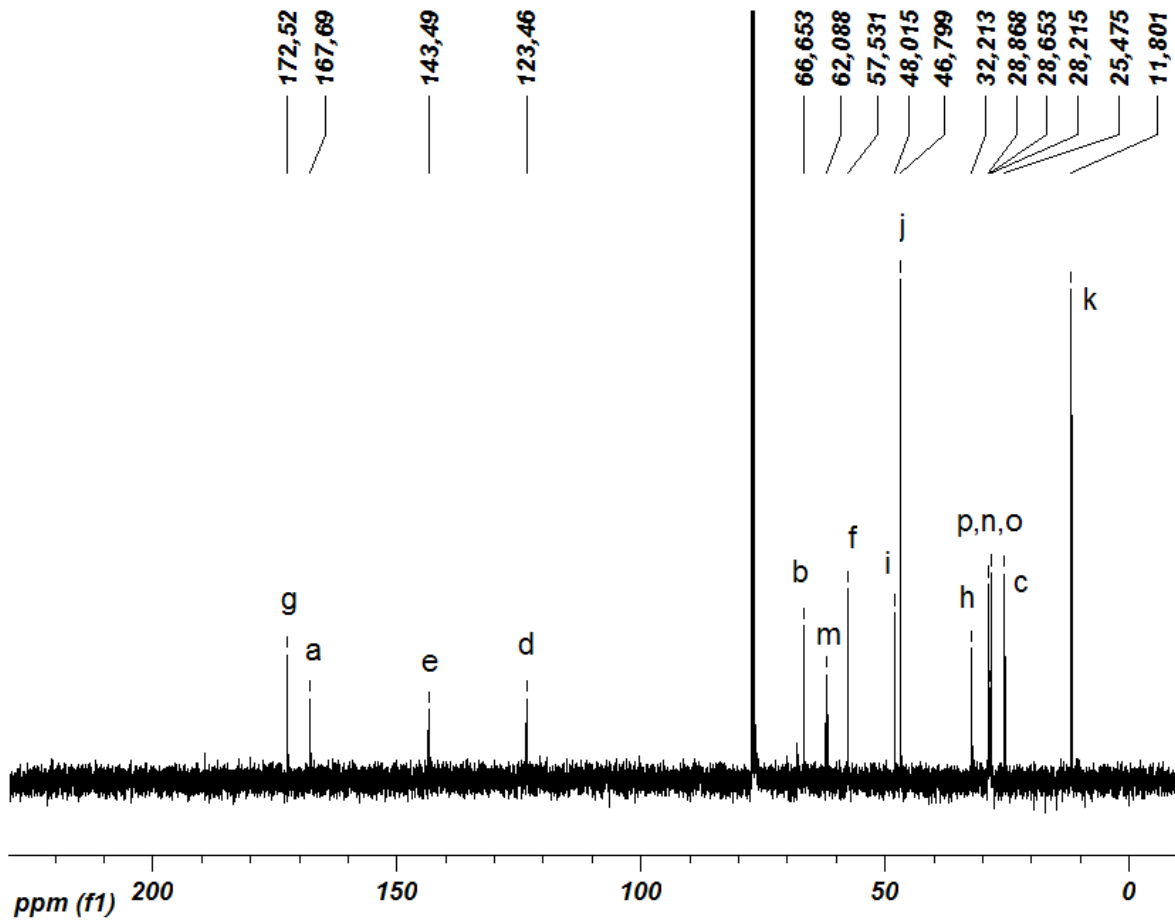
Carbon NMR – Dimethylamine-grafted polyester



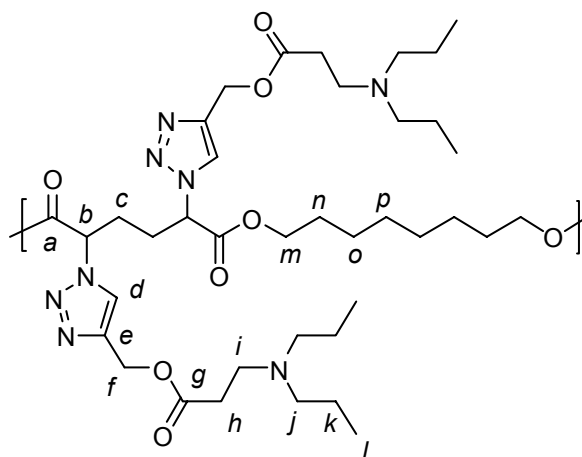
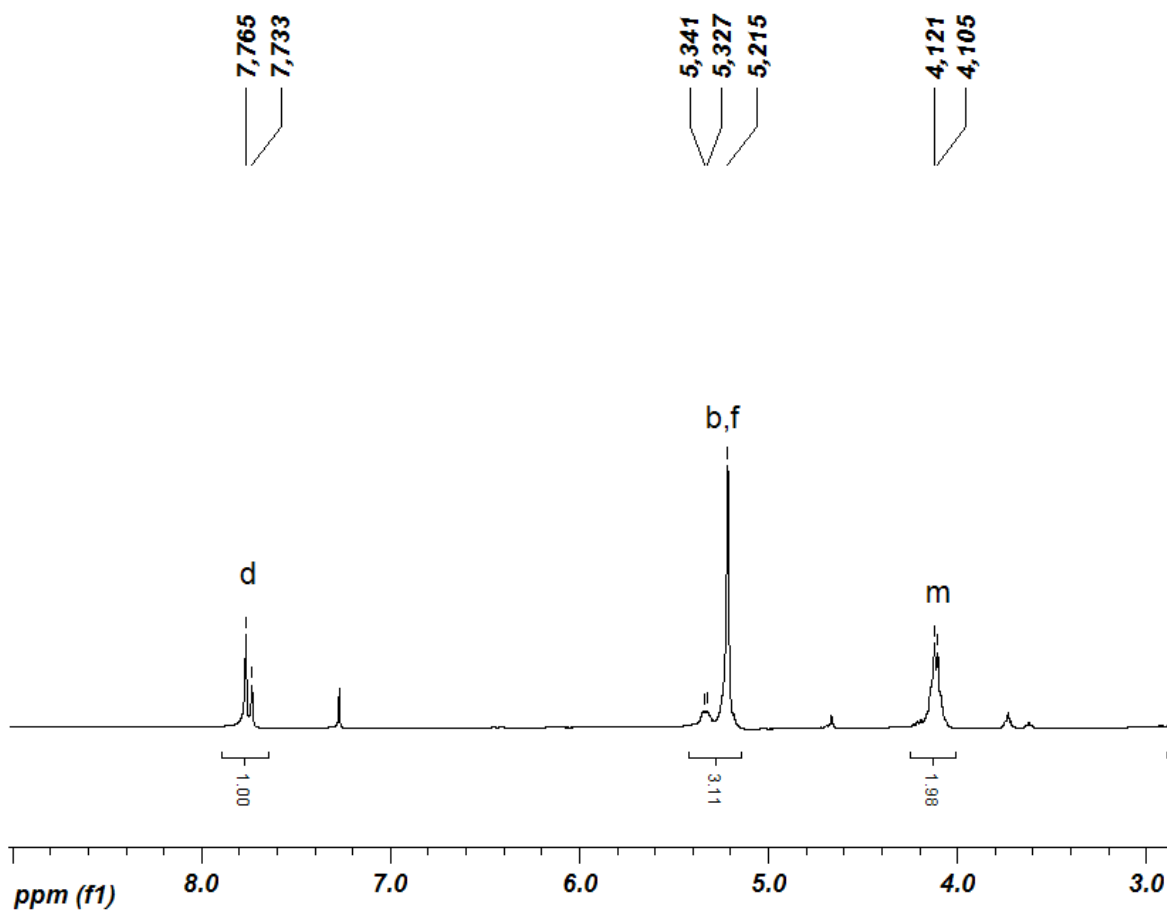
Proton NMR – Diethylamine-grafted polyester



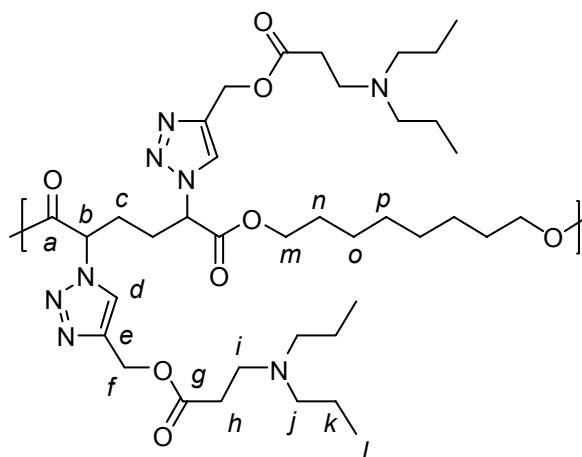
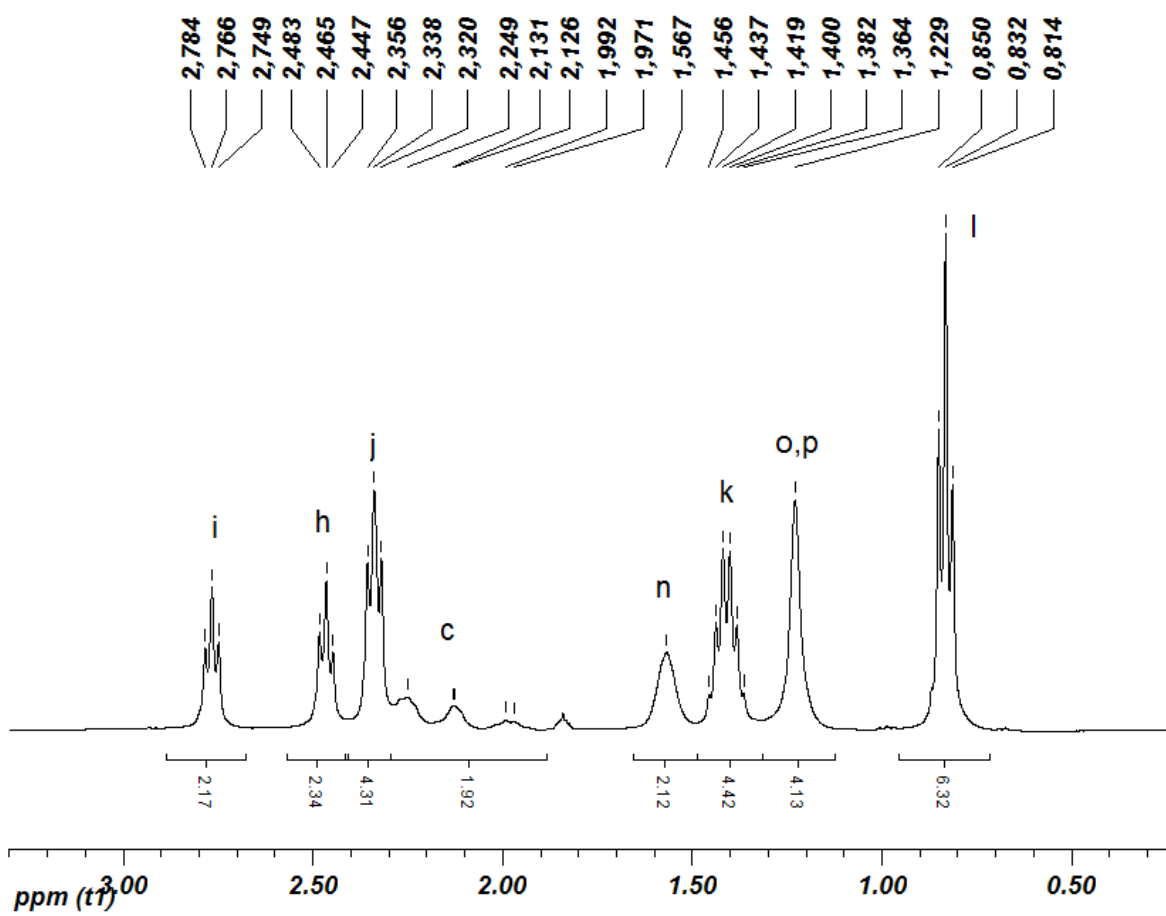
Carbon NMR – Diethylamine-grafted polyester



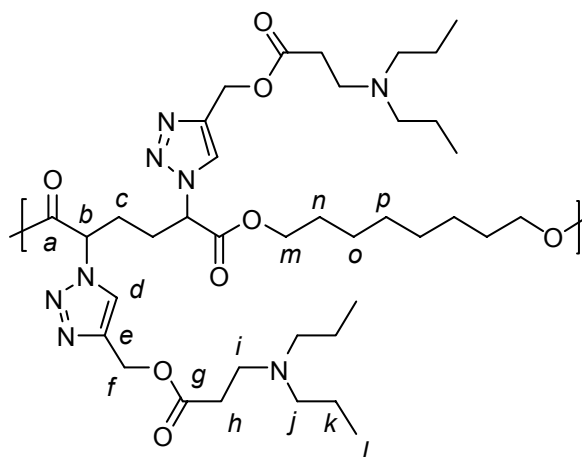
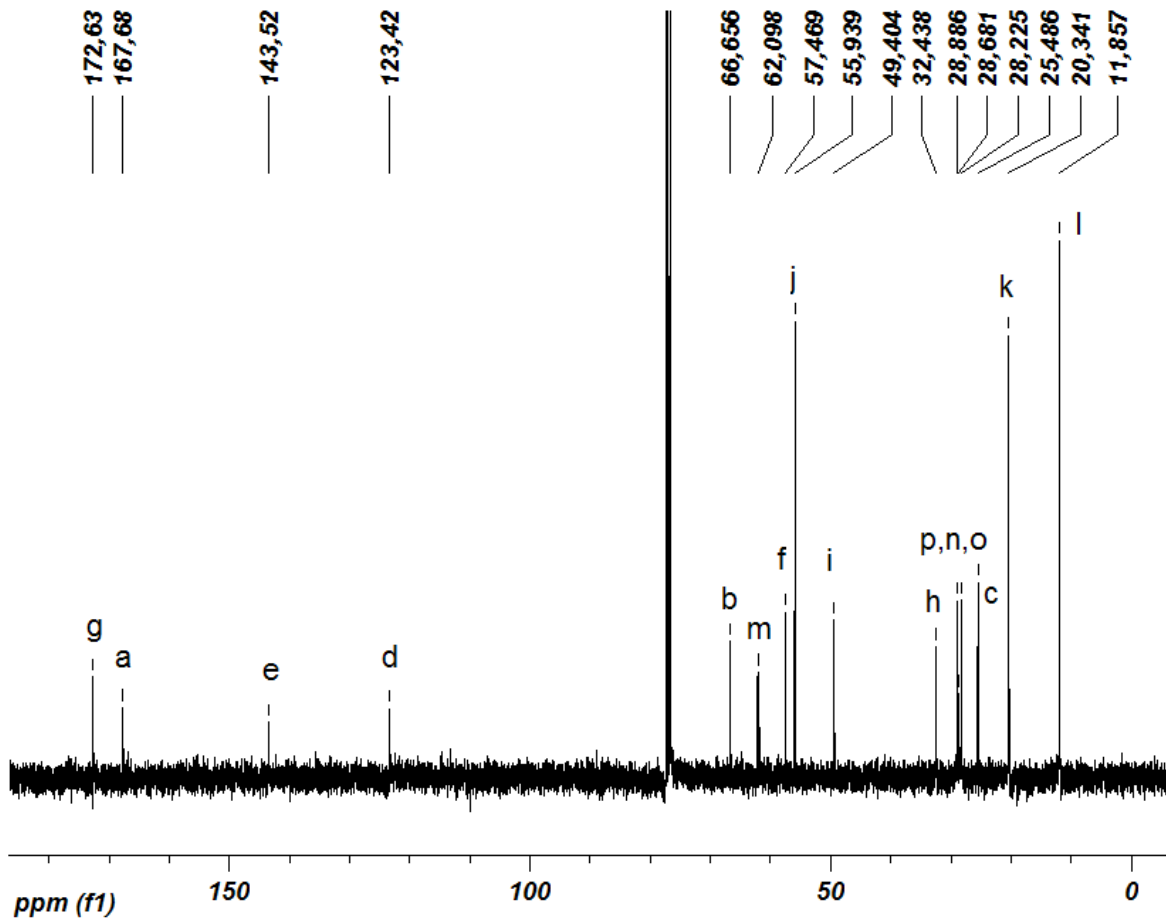
Proton NMR – Dipropylamine-grafted polyester



Proton NMR – Dipropylamine-grafted polyester



Carbon NMR – Dipropylamine-grafted polyester

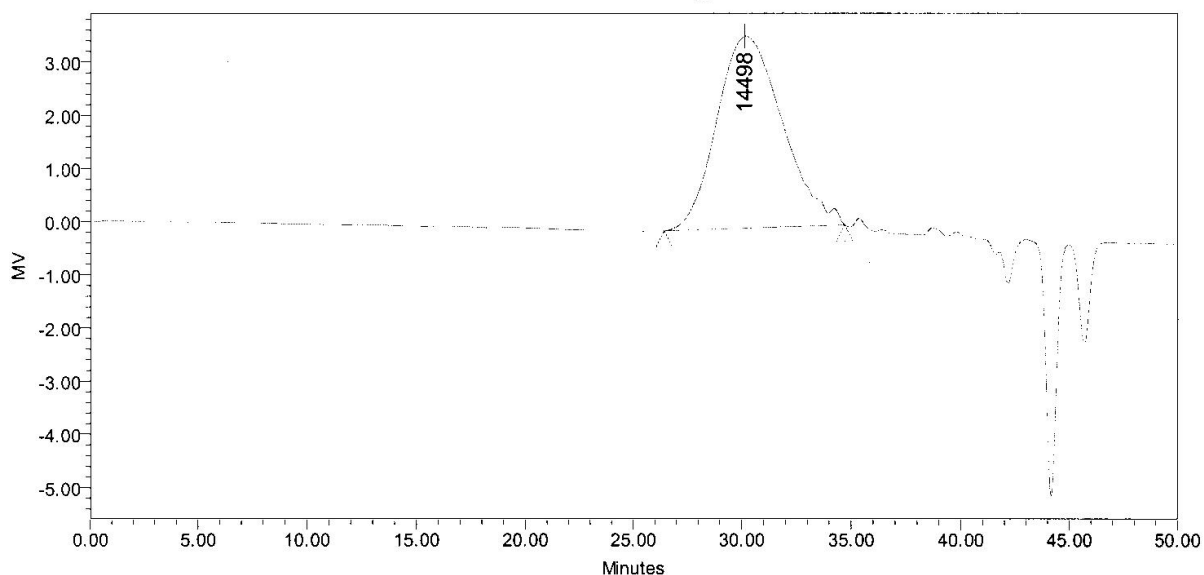




SAMPLE INFORMATION

Sample Name:	ab6-17 net3	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	080404
Vial:	17	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 ul	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired: 4/4/2008 12:38:21 PM EST			
Date Processed: 4/4/2008 3:57:37 PM EST			

Auto-Scaled Chromatogram



GPC Results

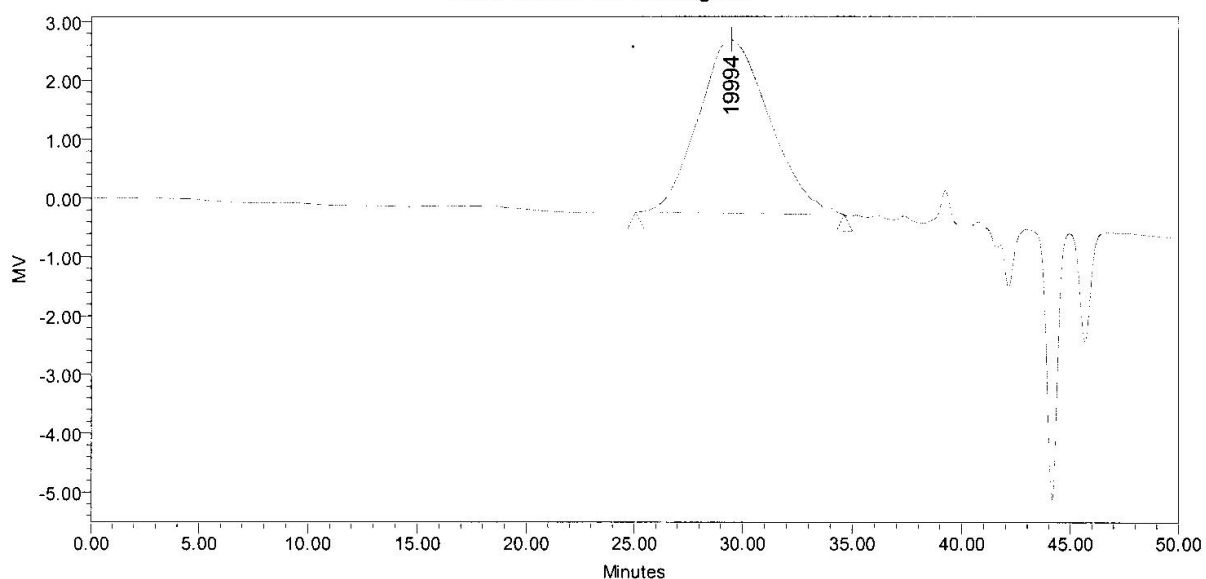
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Poly dispersity	K	alpha
1		9474	15283		14498	22306	29971	1.613142		



SAMPLE INFORMATION

Sample Name:	ab6-18 net3	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	080404
Vial:	18	Acq. Method Set:	GPC FDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 μ l	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	4/4/2008 1:29:47 PM EST		
Date Processed:	4/4/2008 3:57:54 PM EST		

Auto-Scaled Chromatogram



GPC Results

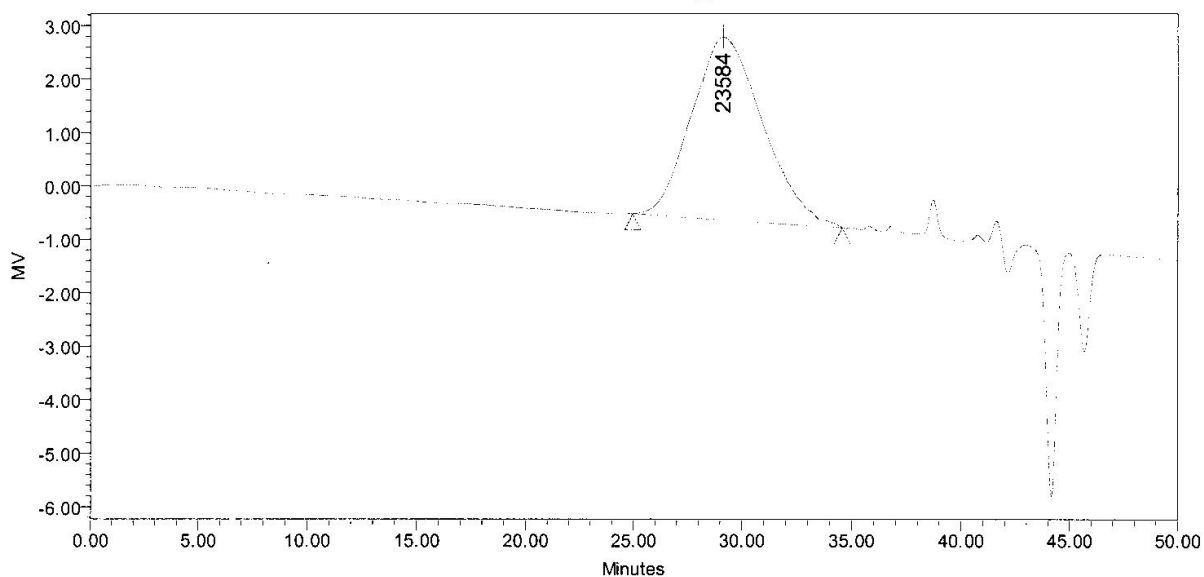
	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Poly dispersity	K	alpha
1		13535	23741		19994	38053	55504	1.754043		



SAMPLE INFORMATION

Sample Name:	ab6-19 net3	Acquired By:	System
Sample Type:	Broad Unknown	Sample Set Name:	080404
Vial:	19	Acq. Method Set:	GPC PDA Off
Injection #:	1	Processing Method:	070412 THF
Injection Volume:	100.00 μ l	Channel Name:	410
Run Time:	50.0 Minutes	Proc. Chnl. Descr.:	
Date Acquired:	4/4/2008 2:21:12 PM EST		
Date Processed:	4/4/2008 3:58:07 PM EST		

Auto-Scaled Chromatogram



GPC Results

	Dist Name	Mn	Mw	Mv	MP	Mz	Mz+1	Polydispersity	K	alpha
1		15064	27045		23584	43326	62510	1.795356		

DSC – Dimethylamine-grafted polyester

<< DSC >>

Data Name: AB5-90

Date: 8/ 1/ 9 10:05

Sample: AB5-90

10.6 mg

Reference: Al

0 mg

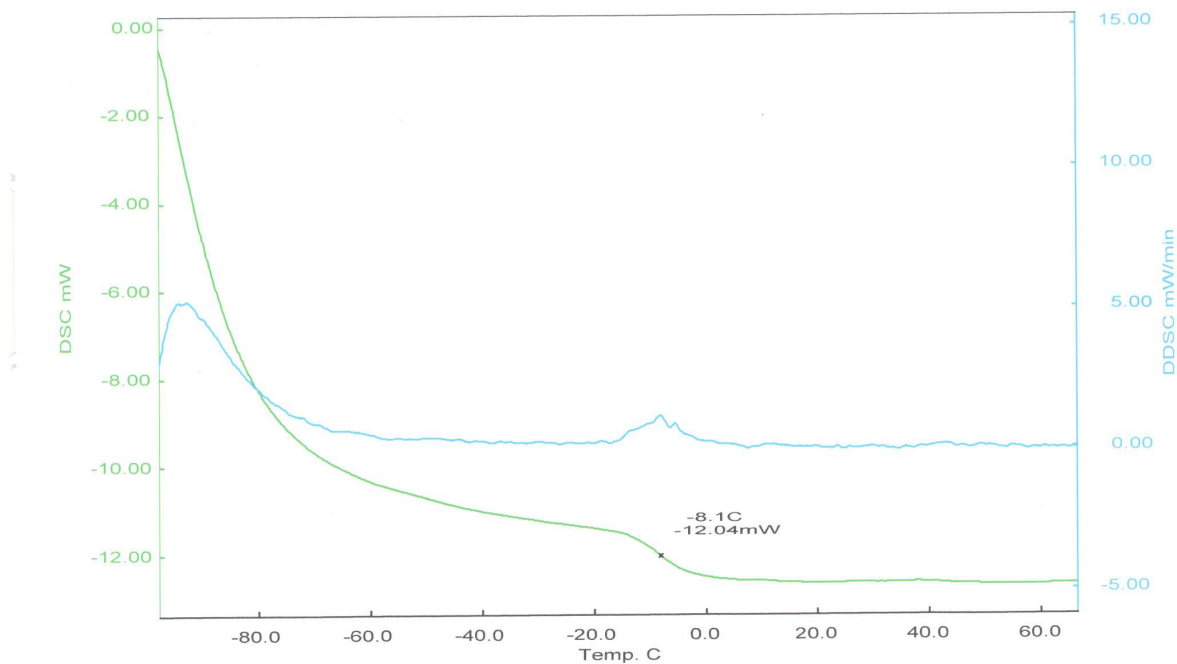
Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25 - 75	10	5	0.5
2*	75 - -100	10	10	0.5
3*	-100 - 75	10	5	0.5
4*	75 - 25	10	1	0.5

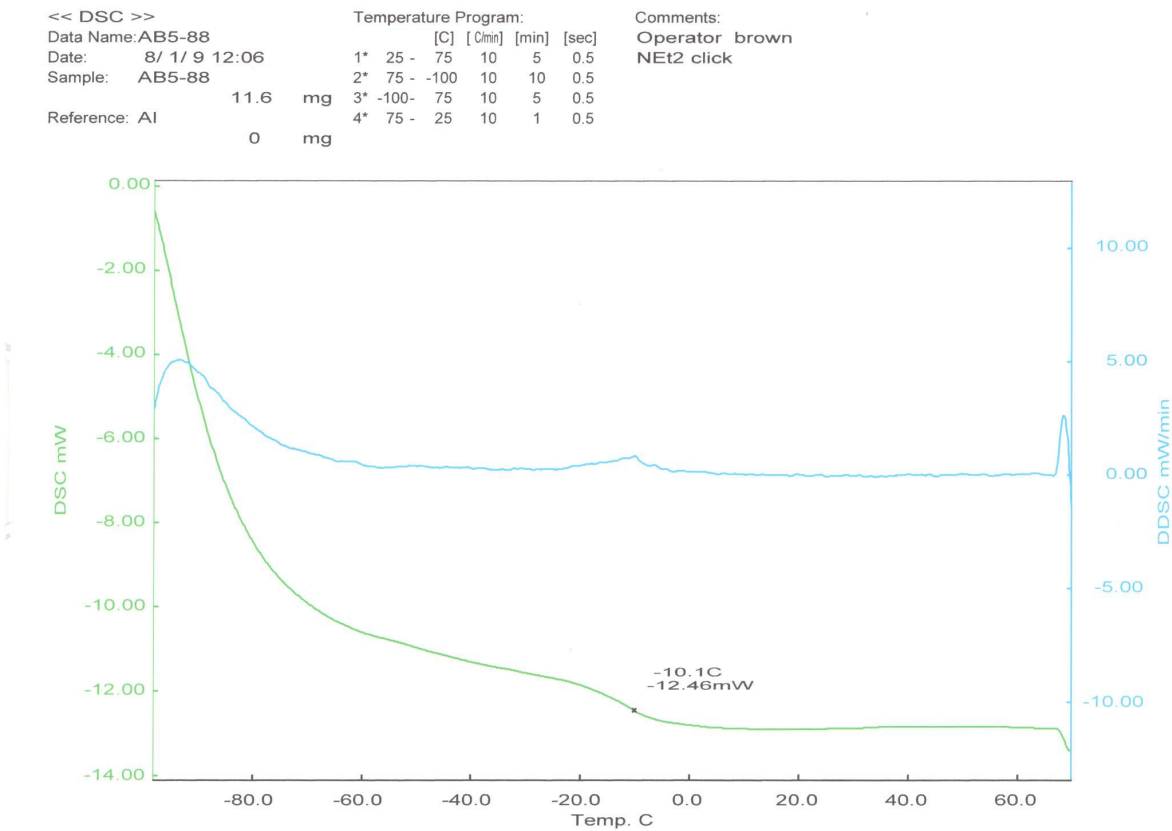
Comments:

Operator brown

NMe2 click



DSC – Diethylamine-grafted polyester



DSC – dipropylamine-grafted polyester

<< DSC >>

Data Name: AB5-89

Date: 8/ 1/ 9 13:20

Sample: AB5-89

Reference: Al

11.9 mg

0 mg

Temperature Program:

	[C]	[C/min]	[min]	[sec]
1*	25 - 75	10	5	0.5
2*	75 - -100	10	10	0.5
3*	-100 - 75	10	5	0.5
4*	75 - 25	10	1	0.5

Comments:

Operator brown

NPr2 click

